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Clinical features of neurological patients with coronavirus 2019: an observational study of one centre

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ABSTRACT

Background. Since the emergence of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) in Wuhan, China, it has been extensively studied by many scientists. Susceptibility to SARS-CoV-2 infection is shown by people of all ages, especially those with different comorbidities. Our goal was to describe the clinical characteristics, treatment, course, and outcome of COVID-19 in patients with pre-existing neurological disorders.

Materials and methods. We retrospectively studied 70 patients with COVID-19 and previous neurological diseases who were treated in the Central Clinical Hospital of the Ministry of the Interior and Administration from 16 March to 15 June 2020. Demographic data, symptoms, image data, laboratory results, treatment methods and results, clinical signs and symptoms of patients hospitalised due to CNS diseases with COVID-19 were collected.

Results. The average age of hospitalised patients was 72, and the majority (63%) were women (44/70). The most common neurological disease was dementia, which was present in almost a third of patients (30.76%), followed by ischaemic stroke (24.61%). Chest imaging showed the presence of interstitial changes in 47% (33) of patients. Laboratory tests revealed increased total blood cells, increased levels of C-reactive protein, procalcitonin, D-dimers, liver indicator markers and IL-6 in the most severely affected patients. The treatment of patients was focused on monitoring their clinical condition, and supporting respiratory inefficiency with passive oxygen therapy and mechanical ventilation. According to the guidelines of the Hospital Therapeutic Committee, pharmacological treatment (Arechin®, Kaletra®) was introduced in cases without contraindications. In patients with moderate COVID-19, antimalarial or antiviral agents were applied (78%). 30% of our observed patients died during the hospitalisation.

Conclusions. We studied a select group of patients (elderly, with comorbidities, and moderate or severe COVID-19 course). Pre-existing neurological disorders were additionally associated with a poorer prognosis and a high fatality rate (30%). Dementia and CNS vascular disorder were the most frequent pre-existing neurological conditions. The neurological symptoms of COVID-19 were various. We observed impaired consciousness, dizziness, headache, nausea, myalgia, psychomotor agitation and slowness, delirium, and psychoses. Further analysis is needed to elucidate the incidence of COVID-19 neurological complications.

Key words: coronavirus, COVID-19, SARS-CoV-2, dementia, stroke

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Introduction

Coronavirus disease 2019 (COVID-19) led to a global pandemic within just a few months of the first outbreak in humans in the city of Wuhan, China in December 2019 [1].

As yet, no concise recommendations based on randomised clinical trials for the management of patients with COVID-19 have been proposed. Therefore the procedure for infected patients remains a challenge. Patients with COVID-19 may present multi-organ insufficiency, including central nervous system involvement. The treatment is complicated by the fact that patients, especially the elderly, may have multiple comorbidities.

The goal of this retrospective study was to present the clinical characteristics, course and outcome of patients with both COVID-19 and coexisting neurological problems.

Materials and methods

Patients

We analysed 70 patients with neurological disorders and diagnosed COVID-19. The patients were hospitalised in the Department of Neurology between 16 March and 15 June 2020 in the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland, a tertiary multispecialty hospital. This hospital was declared a designated infectious disease centre as part of the general healthcare system reorganisation programme in response to the pandemic.

Patients were admitted either directly from the emergency department, outpatient clinics, or external hospitals. The reasons for admission were moderate or severe COVID-19 or SARS-CoV-2-positive patients with other severe concomitant acute or chronic diseases. Infections were confirmed using real time PCR in all patients prior to admission by detecting the genetic material of the SARS-CoV-2 virus in a nasopharyngeal swab. The Modified Early Warning Scale (MEWS) was used to assess the clinical status of the COVID-19 patients (in particular, monitoring of respiratory function), and the widely used Glasgow Coma Scale (GCS) was used to monitor the patient's state of consciousness (Tab. 1).

Collected data

Demographic data, clinical features, infection exposure history, estimated incubation period, signs and symptoms of the disease, computed tomography (CT) or X-ray results, complications, treatment, clinical results and the laboratory results of each patient were obtained from the electronic system of the medical documentation of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw. The date of disease onset, COVID-19 smear, hospital admission, duration of illness, and family history of exposure were recorded. Each patient on admission, and before discharge, had a laboratory test including blood count, serum biochemistry (C-reactive protein, procalcitonin, aspartate aminotransferase, alanine aminotransferase, creatine kinase, creatinine and D-dimer), and IL-6. Patients who required monitoring of laboratory parameters due to deterioration of their clinical status had the necessary procedures performed as appropriate.

Ethics

This study was approved by the Local Ethics Committee of the Central Clinical Hospital of the Ministry of the Interior and Administration (CSK-05/06/2020).

Results

Demographic characteristics of COVID-19 patients

All patients were hospitalised in the CSK MSWiA in Warsaw following its transformation into a COVID-19-dedicated hospital. We included 70 patients in the study group. The average age was 72. The majority of patients were women (65.4%). Fourteen patients were residents of nursing homes. 53 patients were initially hospitalised in other mainly neurological departments outside the CSK MSWiA or were transferred directly from emergency wards after the diagnosis of COVID-19. All these patients had had close contact with confirmed or suspected COVID-19 patients. Only three patients were admitted directly from their homes: their transmission route was unclear. The duration of the disease in all patients was 18 days on average (time from positive RT PCR to obtaining the first negative RT PCR). Four patients had a significantly

Table 1. Modified early warning score (MEWS)

Score	3	2	1	0	1	2	3
Systolic blood pressure	< 70	71–80	81–100	101–199			
Heart rate		< 40	41–50	51–100	101–110	111–129	> 130
Temperature		< 35		35–38.4		> 38.5	
Respiratory rate		< 9		9–14	15–20	21–29	> 30
Level of consciousness				Alert	Voice	Pain	Unresponsive

Contact physician when MEWS score > 4, if oxygen saturation drops < 90% with oxygen treatment, and if you are concerned about the patient's condition

Table 2. Demographics, baseline and symptoms of patients with coronavirus disease 2019 (COVID-19)

Characteristics	
Age (years)	71.68
Sex (M:F)	26:44
Disease duration (days)	18
Symptoms	
Fever, n (%)	32 (45.71%)
Cough	14 (20%)
Fatigue/myalgia	15 (21.42%)
Headache	12 (17.14%)
Expectoration	3 (4.28%)
Nausea/vomiting	7 (10%)
Diarrhoea	6 (8.57%)
Constipation	2 (2.85%)
Dizziness	15 (38.57%)
Dyspnoea	27 (50%)
Chest CT/X-ray	25/45
Unilateral pneumonia	10 (14.28%)
Bilateral pneumonia	27 (40.0%)
Death, n (%)	21 (30.0%)

longer elimination period for coronavirus RNA compared to the others (34, 35, 55 and 66 days). Twenty-one of the hospitalisations were fatal, which gave a mortality rate of 30%.

Clinical characteristics and chest imaging results

In our patients, the most common symptom was fever (59.6%), followed by shortness of breath (50%), cough (25%), muscle pain (19.2%), dizziness (19.2%), headache (17.14%), vomiting (13.5%), diarrhoea (11.5%), and constipation (2%) (Tab. 2). COVID-characteristic abnormalities in the chest tomography (CT) or X-ray (Tab. 2) were observed in most patients. Eight patients had unilateral pneumonia, and 25 (36%) had bilateral pneumonia. Imaging changes included interstitial compaction, 'frosted glass' or 'honeycomb' areas, and exudate.

Sepsis occurred in four patients, and complications of treatment with features of acute pancreatitis was observed in three patients treated with ritonavir/lopinavir (Kaletra®). Among all the patients, we noted four cases of pulmonary embolism. After treatment with low-molecular-weight heparin, the embolic material completely resorbed, which was confirmed by CT angiography of the chest.

Evaluation of laboratory tests

All patients hospitalised in our centre had SARS-CoV-2 infection confirmed by RT-PCR. We noted increased levels of C-reactive protein (CRP), increased alanine aminotransferase (ALT) and asparagine aminotransferase (AST) (Tab. 3). Thirty-two patients had increased D-dimers levels. IL-6 was elevated in 18 patients. All patients who died had significantly

Table 3. Laboratory tests of patients with coronavirus disease 2019 (COVID-19)

Variables	Value
Leucocytes (normal range 4–10 x 10^3 /µL)	9.07 (4.07–28.06)
Thrombocyte (normal range 130–350 x 10^3/µL)	222.25 (98–374)
Haemoglobin (normal range 14–18 g/dL men, 12–16 g/dL women)	12.84 (7–18.5)
C-reactive protein (normal range < 10 mg/L)	52.62 (0.4–191.4)
Aspartate aminotransferase (normal range 5–50 U/L)	39.1 (13–110)
Alanine aminotransferase (normal range 5–50 U/L)	34.1 (8–159)
Creatine kinase (normal range 24–195 IU/L)	293.8 (14–5,089)
Creatine (normal range 0.6–1.3 mg/dL)	1.13 (0.39–8.25)
D-dimer (normal range < 500 mg/L)	2,619 (149–31,128)
IL-6 (normal range < 7 pg/mL)	60.22 (2.02–369)
Procalcitonin (normal range < 15 ng//mL)	0.41 (0.02–4.26)

Table 4. Treatment of neurological patients with coronavirus disease 2019 (COVID-19)

Variables	No (%)
Oxygen therapy	40 (61.53)
Mechanical ventilation	4 (5.71)
Antibiotic treatment	
— Azithromycin	30 (42.85)
— Ceftriaxone	31 (44.28)
Chloroquine	52 (74.28)
Antiviral treatment (lopinavir + ritonavir)	9 (12.85)

higher mean inflammatory parameters in relation to the group of convalescents: CRP (82.50 *vs.* 49.86 mg/L), PCT (1.16 *vs.* 0.48 ng/mL), and IL-6 (184.44 *vs.* 72.4 pg/mL).

Treatment and results

Treatment methods during the SARS-CoV-2 pandemic have changed over time due to the accumulated experience of many researchers worldwide. Initially, all patients who had no contraindications received chloroquine. Patients with pneumonia were additionally administered ceftriaxone and/or azithromycin. Hydrocortisone was the next treatment option given to patients with a moderate or severe course. Patients with inadequate oxygen saturation were administered low and slow flow oxygen supplementation. COVID-19 treatment continued to focus on a symptomatic approach and respiratory support (Tab. 4). Of the 70 patients, 40 received high-flow oxygen therapy, while four underwent mechanical ventilation after being transferred to the Intensive Care Unit. Two of these four died.

Most patients (74.28%) received chloroquine. If signs of pneumonia appeared, azithromycin (30/70) and/or ceftriaxone (31/40) were added. After chloroquine treatment failure, nine

Table 5. Common neurological diseases and co-morbidities of patients with coronavirus disease 2019 (COVID-19)

Neurological disease	No (%)	Other accompanying disease	No (%)
Dementia	22 (31.42)	Arterial hypertension	36 (51.42)
Ischaemic stroke	17 (24.28)	Tumour	18 (25.71)
Ischaemic stroke – subacute phase	11 (15.71)	Tumour – mild	2 (2.85)
Ischaemic stroke – chronic phase	6 (9.23)	Tumour – malignant	16 (22.85)
Malignant tumour CNS	9 (12.85)	Diabetes mellitus	13 (18.57)
Intracerebral haemorrhage	5 (7.14)	Heart failure	13 (18.57)
Craniocerebral trauma	7 (10)	Atrial fibrillation	11 (15.71)
Epilepsy	4 (5.71)	Dyslipidaemia	10 (14.28)
Subarachnoid haemorrhage	3 (4.28)	Renal failure	9 (13.84)
Multiple sclerosis	2 (2.85)	Chronic obstructive pulmonary disease	5 (7.14)
Polyneuropathy	2 (2.85)	Hypothyroidism	5 (7.14)
Myasthenia	1 (1.42)	Prostatic hyperplasia	5 (7.14)
Parkinson's Disease	2 (2.85)	Bronchial asthma	4 (5.71)
Essential tremor	1 (1.42)		

patients received lopinavir in combination with ritonavir. Seven of these nine patients died, and three demonstrated early complications in the form of biochemical features of pancreatitis. Intravenous glucocorticoids were instituted as adjunctive therapy in brain tumours; other pharmaceuticals were used according to the patient's condition/other comorbidities.

ECG assessment – QTc

We estimated QTc interval in ECG at the beginning of hospitalisation. Prolongation of the QTc interval was observed in 21.4% of patients before introducing chloroquine and/or azithromycin. This prolongation was borderline or connected with a bundle branch block (mainly RBBB) or the presence of a stimulator (QRS > 120 ms), so we did not postpone therapy. During our observation, we noticed a prolongation of QTc interval in all of the previously prolonged QTc cases. In some cases, we stopped therapy with medicines that influenced the duration of the QTc interval. In some, we estimated the QTc interval every day and continued therapy.

Only in 7.1% of patients with correct QTc interval before treatment did we observe a prolongation of the QTc interval during such therapy. The maximal QTc interval in these cases was 480 ms.

We did not observe any serious ventricular arrythmias including torsade de pointes.

Death analysis

In relation to the entire study population, the average age of the patients with a fatal outcome was significantly higher (71.68 *vs.* 81.86; p = 0.012), but the group was still dominated by women. Almost half of the patients (10/21) who died suffered from severe dementia. Six patients were hospitalised with concomitant ischaemic stroke. All of them were admitted outside the thrombolytic/thrombectomy window. The other neurological conditions associated with COVID-19 were: multiple sclerosis (1/21), essential tremor (1/21), and malignant tumour with CNS metastases (3/21). A high percentage of deaths (30%) was associated with comorbidities other than neurological diseases. These comorbidities significantly influenced the course of SARS-CoV-2 infection. Eleven out 21 patients had atrial fibrillation, 6/21 patients had type 2 diabetes, five patients suffered from chronic kidney disease stage 4; one was in stage 5 on dialysis. Hypertension was present in all patients with a fatal outcome.

All patients who died had significantly increased mean inflammatory parameters. Compared to the whole studied group, the following parameters were increased: CRP (80.49 *vs.* 52.62 mg/L), PCT (0.66 *vs.* 0.41 ng/mL), and IL-6 (141.24 *vs.* 60.22 g/mL). Coagulation parameters were also elevated (mean D-dimer 4,367 *vs.* 2,619 µ/L) with normal mean platelet values (215.57 *vs.* 222.25 thousand/µL).

50% of patients whose hospitalisation ended with death had bilateral pneumonia and/or fever (11 *vs.* 22 and 11 *vs.* 22). The abovementioned neurological and non-neurological comorbidities, advanced age, and coexisting SARS-CoV-2 infection all contributed to the high percentage of deaths.

Neurological diseases in patients with COVID-19

All patients hospitalised in our Department were admitted due to SARS-CoV-2 infection and co-existing neurological disease. Fifteen patients admitted to our centre were initially asymptomatic for COVID-19, of whom five developed symptoms of pneumonia.

Dementia was the most common disorder, present in 30.61% of patients (Tab. 5). Patients with dementia were older in relation to the whole study population (78.61 *vs.* 71.68), and all of them had a number of comorbidities that negatively influenced the prognosis.

Fever (12/22), myalgia (5/22), and headache (3/22) were the most common symptoms that accompanied SARS-CoV-2 infection in the dementia group. Fifteen patients developed pneumonia accompanied by dyspnoea.

Ischaemic stroke was the second most frequent disease (16 patients with SARS-CoV-2 infection) (Tab. 5). Ten of them were admitted to the hospital in a subacute phase. None of our patients with ischaemic stroke were admitted to our centre in the therapeutic window, while four patients were transferred after thrombolysis at other centres.

Ischaemic stroke was mainly caused by thrombosis/embolism in intracerebral arteries, in 17 patients. In nine patients, there was coexistence with hypertension, dyslipidaemia, type 2 diabetes, and current smoking. Cardiogenic mechanism of stroke could be suspected in 6/17 patients (arrhythmias, atrial fibrillation). The remaining patients had end-stage renal failure and disseminated neoplastic disease.

The above data may suggest that the coexistence of SARS--CoV-2 infection and stroke was rather accidental, and that infection was not the cause of ischaemic stroke. D-dimer is an important parameter in stroke and COVID-19. D-dimer levels were five times their normal value in patients with both stroke and COVID-19. 7/17 ischaemic stroke patients had fully symptomatic pneumonia which necessitated oxygen supplementation. In six patients, SARS-CoV-2 infection was asymptomatic, and in the remaining patients headache, fever and cough were present.

In one patient with epilepsy, the infection caused cluster seizures. The remaining three patients with chronic epilepsy did not present any seizures during hospitalisation.

Less frequent cases included cerebral haemorrhagic stroke, CNS malignant tumour, and craniocerebral trauma (Tab. 3).

We have not observed any significant impact (e.g. worsening of symptoms) of SARS-CoV-2 infection on the coexisting neurological disorder. The described neurological symptoms resulting from headache, nausea, dizziness and myalgia are related to all viral infections, just as with COVID-19. Nevertheless, in our studied group, these symptoms were mainly present in patients without neurological diseases.

Discussion

Analysis of our patients confirmed the neurological complications of COVID-19 that have been documented in the literature to date [2]. They may involve the central and peripheral nervous systems. We observed ischaemic strokes, haemorrhages and subarachnoid haemorrhages, and epileptic seizures. These findings underline the importance of close neurological monitoring of patients.

The patients with COVID-19 were most commonly hospitalised due to worsening of cognitive function associated with dementia. The severity of these symptoms ranged from headache, dizziness, psychomotor slowness to impaired consciousness. Signs of focal, acute central nervous system involvement was the second most common reason for admission. signs of acute cerebrovascular disease, impaired consciousness to dizziness and headache. Direct infection of CNS (meningitis and encephalitis) with SARS-CoV-2 has been the least frequently reported complication so far. We have not observed direct infection of the central nervous system, which may confirm that this phenomenon is extremely rare [3–5]. However, in the presence of impaired consciousness in the course of e.g. hypocapnia, signs of CNS involvement can be easily missed. These complications require active research and further observation in a larger study group, cerebrospinal fluid assessment and neuroimaging examinations.

We observed that fever was relatively frequent in our patients (45%), while it was present in 20% of patients in other centres [7]. Gastrointestinal symptoms such as nausea and watery diarrhoea were relatively rare and did not exceed 10% of the hospitalised patients. These findings are comparable to other studies [7].

Elevated levels of D-dimers, interleukin-6, ferritin, and lactate dehydrogenase have been documented as part of a cytokine storm in the death rate from COVID-19 [8]. We observed a correlation between the level of the above-mentioned pro-inflammatory markers and the severity of the course of COVID-19. We also noted a direct relationship between the increase of these markers and death. This indicates that the parameters we tested may be considered biomarkers of COVID-19. Similar findings have been reported previously by others [8].

Complications of dementia syndromes

Aggravation of dementia symptoms could be expected. The acute course of COVID-19 may cause complications in the nervous system such as increased cognitive dysfunction, psychosis, psychomotor agitation, depression, and anxiety. Patients with dementia constituted 30% of the studied group. These patients were of advanced age. Considering the severity of the basic disease, COVID-19, and the fact that these patients usually have many comorbidities, this explains the severity of consciousness disorders and delirium [9]. A study conducted by French scientists identified the most common neurological symptoms associated with COVID-19: impairment disturbances of consciousness in 73% of patients, sleep disturbances after discontinuation of sedatives (41%), disorientation (32%), and agitation (9%) [10]. We observed psychomotor agitation only in two patients (2.85%), and wakefulness disturbances after discontinuation of sedatives in approximately 20% of patients.

According to the study of the French ICU, 84% of patients with COVID-19 had abnormalities in neurological examination [11]. Additionally, 15% of patients leaving this department presented symptoms of executive function disorder (concentration and decision-making disturbances, difficulty in controlling behaviour) [11].

Cerebrovascular complications

Cerebrovascular symptoms were much more common in patients with severe SARS-COV-2 infection. They manifested as ischaemic or haemorrhagic stroke. Mao et al. reported that 5.7% of patients with severe COVID-19 developed acute cerebrovascular disease that usually manifested as ischaemic stroke, less commonly as haemorrhagic stroke. [12]. That was also confirmed in our study. Currently, it is believed that the hyperactivation of inflammatory factors is the main cause of clinical deterioration. Hyperactivated neutrophils and macrophages are the source of cytokine storm, which is considered an unfavourable prognostic factor in the disease course [13].

In our analysis, ischaemic stroke was the second most common neurological manifestation, occurring in 15.71% of patients. Four patients underwent thrombolysis in other centres. In the publication by Lodigiani et al., 21% of patients experienced thromboembolic events, including venous thromboembolism, ischaemic stroke, and acute coronary syndrome [14]. The pathomechanism of hypercoagulability in COVID-19 is not entirely understood, but it is believed that an increase of D-dimers may be the cause. In an Italian population of COVID-19 patients with ischaemic stroke, increased levels of D-dimers were noted in 80% of patients. [14]. Similarly, in our group of patients with COVID-19 and stroke, we recorded increased D-dimer in 78% of cases. In addition, as mentioned earlier, the average values of D-dimers in our COVID-19 patients with ischaemic stroke exceeded the norm by up to five times. These values are much higher than those of stroke patients without SARS-CoV-2 infection, and this is believed to be the result of the cytokine storm or hypercoagulable state that occurs in patients with severe COVID-19 [15].

Severe pneumonia in COVID-19 often leads to sepsis-induced hypercoagulability, as evidenced by increased intravascular activation of platelets, increased fibrinogen, and mild prolongation of PT and APTT [16]. Moreover, it is suspected that transient production of antiphospholipid antibodies may play an important role in this mechanism, which is confirmed in the study by Harzallah et al. [17], where almost 45% of patients with confirmed or suspected SARS-CoV-2 infection tested positive for lupus anticoagulants, and five patients had antibodies against cardiolipin or anti-β2-glycoprotein I [17]. In another study by Zhang et al., antiphospholipid antibodies were found in three COVID-19 patients, all of whom had suffered ischaemic strokes in the past [18].

All ischaemic stroke patients hospitalised in our department had multiple comorbidities and potential vascular risk factors, which could result in an unfavourable prognosis, even without coronavirus disease.

Neuromuscular complications

A significant number of patients with neuromuscular diseases are severely physically disabled and may have symptoms of heart, circulatory and/or breathing insufficiency. The course of COVID-19 in these patients may be severe [19].

It has been reported that previously identified human coronaviruses [SARS-CoV-1 and MERS] were associated with Guillain-Barre syndrome [20], but we did not observe acute polyneuropathy.

Among our patients with previously diagnosed neuromuscular diseases (including myasthenia gravis, polyneuropathy), we did not see an exacerbation of the underlying disease resulting from infection. Moreover, none of the patients had respiratory insufficiency or cardiac dysfunction.

Neuromuscular complications due to damage in the course of the applied pharmacotherapy has been already identified [12, 21]. Skeletal muscle injury was defined as muscle pain, elevated serum creatine kinase (CK) (normal value < 170 U/L), ALT, AST, myoglobin. In our research, such complications occurred in 14 patients, but these were only mild and resolved spontaneously.

Epilepsy complications

Four COVID-19 patients in our study were admitted due to epileptic seizures, and one had a complication in the form of cluster seizures. Others had single seizures with good response to pharmacotherapy. According to the publication of Lu et al., in which the authors evaluated 304 COVID-19 patients, none of their patients had symptomatic seizures or status epilepticus [22]. Due to the fact that we still have limited knowledge about the impact of SARS-CoV-2 on epilepsy, and because of polypharmacy, these patients may require increased vigilance and more frequent EEG tests or periodic continuous monitoring in selected cases [23].

Conclusions

We had a selected group of patients. They were elderly, often with comorbidities and moderate or severe COVID-19 course. Additionally, coexisting neurological diseases also significantly contributed to the course of the disease, causing a high fatality rate (30%). In this studied group, dementia and CNS vascular disorders were the most frequent pre-existing neurological conditions. Increased inflammatory parameters were directly associated with more severe course of COVID-19. This may be due to a direct cytopathic effect of the virus, inflammatory response, and/or hypercoagulable state.

Neurological symptoms of COVID-19 are not uncommon. We observed impaired consciousness, dizziness, headache, nausea, myalgia, psychomotor agitation and slowness, delirium, and psychoses. We did not observe direct CNS involvement (encephalitis, encephalopathy), which is increasingly being reported in the literature. Further analysis is needed to elucidate the incidence of COVID-19's neurological complications.

Conflict of interest: *The authors declare that they have no competing interests. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest*
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