

New onset neurologic events in people with COVID-19 in 3 regions in China

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Abstract

Objective

To investigate new-onset neurologic impairments associated with coronavirus disease 2019 (COVID-19).

Methods

A retrospective multicenter cohort study was conducted between January 18 and March 20, 2020, including people with confirmed COVID-19 from 56 hospitals officially designated in 3 Chinese regions; data were extracted from medical records. New-onset neurologic events as assessed by neurology consultants based on manifestations, clinical examination, and investigations were noted, in which critical events included disorders of consciousness, stroke, CNS infection, seizures, and status epilepticus.

Results

We enrolled 917 people with average age 48.7 years and 55% were male. The frequency of new-onset critical neurologic events was 3.5% (32/917) overall and 9.4% (30/319) among those with severe or critical COVID-19. These were impaired consciousness (n = 25) or stroke (n = 10). The risk of critical neurologic events was highly associated with age above 60 years and previous history of neurologic conditions. Noncritical events were seen in fewer than 1% (7/917), including muscle cramp, unexplained headache, occipital neuralgia, tic, and tremor. Brain CT in 28 people led to new findings in 9. Findings from lumbar puncture in 3 with suspected CNS infection, unexplained headache, or severe occipital neuralgia were unremarkable.

Conclusions

People with COVID-19 aged over 60 and with neurologic comorbidities were at higher risk of developing critical neurologic impairment, mainly impaired consciousness and cerebrovascular accidents. Brain CT should be considered when new-onset brain injury is suspected, especially in people under sedation or showing an unexplained decline in consciousness. Evidence of direct acute insult of severe acute respiratory syndrome coronavirus 2 to the CNS is lacking.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

COVID-19 = coronavirus disease 2019; **GCS** = Glasgow Coma Scale; **ICU** = intensive care unit; **IMV** = invasive mechanical ventilation; **NIPPV** = noninvasive positive-pressure ventilation; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

A cluster of cases of pneumonia of unknown cause was reported in Wuhan, China, in December 2019. The city became the epicenter of the first outbreak of what would become known as coronavirus disease 2019 (COVID-19), caused by a novel type of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak quickly evolved into a global pandemic.

People with COVID-19 present with a wide spectrum of symptoms, of which the most frequent are fever, dry cough, and shortness of breath. Many patients also report nonspecific symptoms of fatigue, headache, and myalgia,^{1,2} which are presumably due to the systemic disorder and usually resolve without specific treatment.

The presence of new-onset neurologic impairment requiring investigation and intervention remains largely unknown in people with COVID-19, apart from 2 single-center reports and some case reports.^{3–12} Studies of another human coronavirus, the severe acute respiratory syndrome coronavirus, have suggested the possibility that it can directly cause acute or subacute neurologic impairment.^{13–15}

We ascertained new-onset neurologic events during the acute phase of COVID-19. This may help clinicians optimize treatment and management of such individuals, improving their prognosis.

Methods

Ethics

The study was approved by the Ethics Board of West China Hospital, Sichuan University (approval 2020[100]). Due to the circumstances and the retrospective nature of the study, the need for informed consent was waived provided data were anonymized.

Participants

We conducted the study in 56 hospitals officially designated as COVID-19 treatment centers from 3 jurisdictions: Wuhan, Hubei province's capital (and the epicenter); Chongqing municipality, which borders Hubei province; and Sichuan province, which borders Chongqing but not Hubei. E-table-1 in the appendix (doi.org/10.5061/dryad.nk98sf7qx) provides a list of participating hospitals and the number of people reported by each.

People admitted who met the agreed national guideline (Chinese national guideline, 6th edition) for symptomatic

COVID-19 were enrolled consecutively.¹⁶ In Sichuan and Chongqing, enrollment was between January 18 and March 3, 2020, and in Wuhan, between January 18 and March 20, 2020. People (n = 304) in this cohort enrolled prior to February 18, 2020, were reviewed for seizure-related incidents and this subgroup of the cohort was previously reported elsewhere.¹⁷

Diagnosis was based on the presence of the typical symptoms of fever, cough, and/or typical features on chest CT with a positive identification of SARS-CoV-2 RNA by real-time reverse-transcriptase polymerase chain reaction using the standardized protocol.¹⁶ Those who remained asymptomatic and without CT chest changes were excluded.

Those included were further stratified as having a mild, moderate, severe, or critical condition based on the above guideline (see table 1 for classification criteria).¹⁶

Clinical assessment

A standardized clinical report form was designed to extract data on clinical features, test results, and medical history (e-Methods, doi.org/10.5061/dryad.nk98sf7qx), and investigators completed this form using an online platform (wjx.cn/jq/73405304.aspx). We extracted clinical information from medical notes. In case of uncertainty, attending physicians or neurologists were contacted. The outcome (discharge, death, or still in hospital) was recorded (study-end) for those from Sichuan and Chongqing on March 3 and from Wuhan on March 20, 2020.

An independent neurologist reviewed the notes of people with new-onset neurologic events. We excluded, per protocol, those who only had nonspecific symptoms, such as headache, dizziness, fatigue, and myalgia, presumably likely due to the systemic condition. We also excluded people if their neurologic symptom, such as impaired consciousness, could be fully accounted for by sedation during ventilation. Records of those identified as having had a critical neurologic event were then reviewed and confirmed by 2 other neurologists. We defined new-onset specific neurologic events as those requiring neurologic investigations or interventions.

We further grouped specific new-onset neurologic events into critical and noncritical new neurologic events. We defined critical events as disorders of consciousness, cerebrovascular accidents, CNS infection, seizures, or status epilepticus.

Statistical analysis

Age was normally distributed and reported as mean \pm SD. We assessed intergroup differences in age for significance using

Table 1 Diagnosis and treatment protocol for COVID-19 (trial version 6)¹⁶

Classification	Criteria
Mild	Light clinical symptoms and no sign of pneumonia on lung imaging
Moderate	Fever, respiratory tract symptoms, and other symptoms; imaging suggests pneumonia
Severe	Any of the following: (1) respiratory distress, respiration rate ≥ 30 times/min; (2) oxygen saturation $\leq 93\%$ at rest; (3) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg (1 mm Hg = 0.133 kPa)
Critical	As in severe + any of the following: (1) respiratory failure occurs and mechanical ventilation is required; (2) shock; (3) complicated by other organ failure and need of intensive care unit monitoring and treatment

Student *t* test. Intergroup differences in the frequencies of categorical variables were assessed using χ^2 tests (or Fisher exact test if the values were <5). Variables for multivariable logistic regression on the development of new-onset critical neurologic impairment were selected based on the univariate analysis of the frequency of age over 60, male sex, and non-neurologic/neurologic comorbidities in each group, where *p* value was <0.05 . We considered differences associated with 2-tailed *p* < 0.05 as significant. We performed statistical analyses using Stata 15 for Windows (StataCorp, College Station, TX).

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional ethics board of West China Hospital, Sichuan University (approval 2020[100]).

Data availability

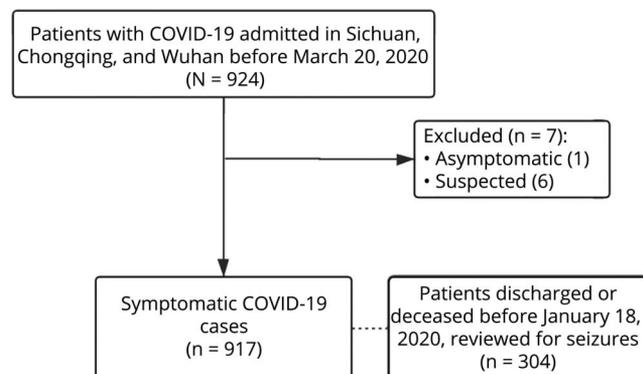
We will share anonymized data by reasonable request from any qualified investigator.

Results

Clinical and demographic

We enrolled 917 people (55% men), comprising 455 from Sichuan, 286 from Wuhan, and 176 from Chongqing (figure 1).

Figure 1 Flowchart of study enrollment



COVID-19 = coronavirus disease 2019.

Data were complete for all assessed variables and outcomes. The mean age was 48.7 ± 17.1 years (range, 3 months to 91 years). Nearly half (404/917, 44%) had non-neurologic comorbidities, and 28 (3%) had neurologic comorbidities. At study end, 742 people had been discharged, 145 were still hospitalized (97 in Sichuan, 1 in Chongqing, and 47 in Wuhan), and 30 had died. A total case-fatality risk of 3.9% (30/772) was seen but was much higher in Wuhan (23/239, 9.6%) than in Sichuan (3/358, 0.8%) or Chongqing (4/175, 2.3%).

After excluding 24 individuals who had depressed levels of consciousness due to sedation, we identified 39 with new-onset neurologic events. Thirty-two of these were critical, and all but 2 of them had severe or critical COVID-19 (tables 2 and 3). This corresponded to a prevalence of critical neurologic events of 3% across all 917 people and 9% among the 319 with severe or critical COVID-19. The prevalence of noncritical events was 0.8%. The equivalent numbers excluding the subgroup (*n* = 304) previously reported were as follows: a prevalence of critical events across 3.4% of the remaining 613 people, and 9.5% among the 211 with severe or critical COVID-19. The prevalence of noncritical events was 0.7%.

New-onset critical neurologic events are detailed in table 3 and table e-2, doi.org/10.5061/dryad.nk98sf7qx).

Disorders of consciousness

Fourteen individuals (age 51–85; 9 male) had disturbance of consciousness, ranging from drowsiness/stupor to coma (Glasgow Coma Scale [GCS] 0–14; 2 people died immediately). Four used oxygen masks and 9 used noninvasive positive-pressure ventilation (NIPPV). Impaired consciousness was attributed to brain insult secondary to septic shock in 5 people, to cardiogenic shock in 3, to hypovolemic shock in 2, to hyperosmolar hyperglycemia in 2, and to cardiac arrest in 1. One died immediately because of cardiac arrest and another died from hypovolemic shock caused by upper gastrointestinal bleeding. A further 8 died between 5 hours and 4 days after deterioration of consciousness. Three who had mild alteration of consciousness (13–14 on GCS) were eventually discharged. The remaining individual with impaired consciousness had cerebral herniation secondary to a preexisting brain tumor and was still hospitalized (GCS 3, 5, 6) at study end.

Table 2 Demographic features of 917 people with COVID-19

Features	Critical neurologic events (n = 32)	No critical neurologic events (n = 885)	p Value
Age, y, mean ± SD	67.6 ± 15.4	48.1 ± 16.8	5.5 × 10 ⁻¹⁰
M/F	19/13	487/398	0.63
Clinical classification, n			
Mild	0	65	1.34 × 10 ⁻²²
Moderate	2	531	
Severe	5	233	
Critical	25	56	
History of non-neurologic conditions, n	17	387	0.29
History of neurologic conditions, n	5	23	2.6 × 10 ⁻⁵
New-onset non-neurologic complications, n	24	418	2.0 × 10 ⁻³

Seven people (30–91 years old; 5 male) had impaired consciousness in the form of nighttime hallucinations, irritability, lack of compliance, inattention, and/or disorganized thinking; 2 had preexisting dementia. Delirium occurred in 2 on NIPPV and in another 2 on invasive mechanical ventilation (IMV). One had ischemic stroke before the delirium (patient 6), and 2 had stroke after the delirium (patients 1 and 5). Six received low-dose dexmedetomidine immediately and 2 underwent tracheotomy due to progressive hypoxemia. At study -end, 1 had recovered and was discharged, 1 died after a possible new-onset stroke (patient 5), and the remaining 5 were still hospitalized under sedation, with scores from -2 to -4 on the Richmond Agitation and Sedation Scale.

Three women between ages 52 and 61 years without a previous history of neurologic or systemic disorders had events

resembling typical syncope with no further complications. ECGs recorded afterwards were normal.

An adult was comatose following traumatic brain injury. On arrival, GCS was 10. Brain CT scan confirmed massive brain injury with a skull fracture. He had recently been in Hubei, was tested, and was positive. He was treated conservatively and mild symptoms including fever and dry cough manifested 2 days later; he made a full recovery and was discharged with only minor neurologic sequelae.

Stroke

Ten people had cerebrovascular accidents (e-table 2, available from Dryad; doi.org/10.5061/dryad.nk98sf7qx). Half had new-onset cardiac arrhythmia (n = 3) or venous thromboembolism (n = 3), and they all had stroke in the late course of

Table 3 Thirty-nine people with new-onset neurologic events

Type of event	Neurologic events		N	Timing of the events (days from the initial symptoms)	Patient no.
Critical (n = 32)	Conscious disturbance (n = 25)	Delirium ^a	7	Mean 12 (range, 4–23)	
		Drowsiness/stupor/coma	14	Mean 12 (range, 1–24)	
		Syncope	3	2, 22, and 27	
		TBI	1	1	
	Stroke ^a (n = 10)	Early onset	2	1 and 6	6, 7
	Late onset	8	Mean 31 (range, 18–48)	1–5, 8–10	
Noncritical (n = 7)	Muscle cramp	2		8 and 16	
	Unexplained headache	2		14 and 19	
	Occipital neuralgia	1		1	11
	Functional? tic/tremor	2		8 and 41	

Abbreviation: TBI = traumatic brain injury.

^aThree had delirium and stroke (patients 2, 6, and 7).

COVID-19. Two individuals (patients 5 and 6) who had strokes early in the course of COVID-19 recovered and were discharged with only minor neurologic sequelae. Of the others, 2 were discharged (patients 8 and 10), 3 died (patients 3–5), and 3 were still hospitalized in a critical condition by study end. Brain CT scans of some of these people (patients 1–4, 8, and 9) are shown in figure 1. None had investigation for possible stroke etiology such as cerebral angiography or coagulation screen.

Others

No acute symptomatic seizures, epileptic seizures, or status epilepticus was seen in the cohort. No case of CNS infection was confirmed in the cohort.

Risk factors of critical neurologic events and outcomes

Univariate analysis identified age above 60 years and neurologic comorbidities as significantly associated with new-onset critical neurologic events, of which only age older than 60 emerged as significant in multivariate analysis (table 4).

Noncritical neurologic events

Occipital neuralgia

Occipital neuralgia was noted in one man (patient 11) in his 40s (table 3). After a cruise he had new-onset, self-limiting paroxysmal burning-like severe pain in his neck that radiated to his scalp. He was only tested for COVID-19 after a contact from the cruise trip tested positive; he then also tested positive. He later developed fever and a cough, and the episodes of occipital neuralgia became more frequent and more intense. On examination, only tenderness of the greater occipital nerve area found and cranial CT and lumbar puncture were unremarkable. Neither the virus nor other pathogens were detected in the CSF. The pain gradually lessened on treatment with pregabalin and he was discharged.

Others

In one person with unexplained severe headache, lumbar puncture was normal and no SARS-CoV-2 was detected.

Neurologic investigations

Brain CT was performed in 28 people and it showed new-onset lesions in 9 (table 5). For those with stroke, detailed findings are provided in e-table 2 (available at doi.org/10.5061/dryad.nk98sf7qx) and figure 2. Lumbar puncture was performed in 1 individual (patient 1) with suspected CNS infection, 1 (patient 11) with occipital neuralgia, and 1 with

unexplained headache. Pressure and routine assays were normal and PCR panel testing for meningitis/encephalitis pathogens and SARS-CoV-2 were negative. No EEG recording or brain MRI was performed in order to decrease potential exposure risk to staff.

Discussion

In this multicenter study, we identified new-onset critical neurologic events including impaired consciousness and cerebrovascular events in fewer than 5% people with COVID-19 and this is compatible overall with a previous report.^{3,5}

We report a lower rate of noncritical or overall neurologic events and this is partly explainable. First, we excluded all nonspecific neurologic symptoms such as headache and dizziness. Second, the previous report was from the epicenter in Wuhan, where higher proportions of people had severe and critical illness.^{3,5} Our cohort included a large number of people from outside Wuhan and only about a third of our sample had severe or critical disease. This may provide a more representative picture of the incidence and spectrum of neurologic manifestations of COVID-19. As we excluded asymptomatic cases, the incidence of neurologic manifestations could have been overestimated. Inclusion of people with preexisting neurologic conditions, such as brain tumors or dementia, might also have overestimated the numbers.

The major factor associated with neurologic complications was age over 60, which was also a strong risk factor for mortality.¹⁸ When we compared people with COVID-19 infections at the same level of severity, new-onset neurologic critical events increased the risk of death by sixfold. Further studies are warranted to investigate the synergistic effect of other known risk factors such as D-dimer greater than 1 µg/L and cardiac injury in people with critical neurologic events.^{18–20}

We also found delirium to be present in nearly a tenth of people with critical disease, and it required prompt intervention. It is lower than the previous reports of people with COVID-19 who experienced delirium while in the intensive care unit (ICU).⁴ Several reasons could explain this. First, early intervention with sedating medications in people on NIPPV or IMV was seen in most; second, the prevalence may differ between populations being evaluated; third, as we did not use screening tools, we may have underdiagnosed delirium. We did not record EEGs. In some people, especially those with a history of epilepsy (none knowingly in the cohort) or findings suggestive of seizures, this could help differentiate delirium from nonconvulsive status epilepticus or focal dyscognitive seizures. We administered dexmedetomidine to most people with delirium and to some who were underventilated, as a precaution.^{21–23} The use of dexmedetomidine in people with COVID-19, however, requires further assessment as well as the true prevalence of delirium in

Table 4 Multivariate logistic regression analysis of new-onset critical neurologic events

Independent variables	OR	p Value	95% CI
Age above 60 years	6.75	0.000	3.01–15.14
Neurologic comorbidities	2.93	0.051	0.99–8.67

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 5 Findings of brain CT in 28 patients

CT indications	Number	New lesions
Headache	2 unexplained and 8 nonspecific	None
Under sedation	6	3 new-onset stroke (patients 1–3)
Stroke	4 (patients 6–8, 10)	3 new-onset stroke
Previous history of stroke	4	1(+) (patient 9)
Occipital neuralgia	1 (patient 11)	None
Declined consciousness due to brain tumor	1	Brain tumor
TBI	1	Frontal epidural hematoma, bilateral frontal lobe contusion and laceration, subarachnoid haemorrhage, multiple fractures of the skull base, frontal, and parietal bone
Syncope	1	None

Abbreviation: TBI = traumatic brain injury.

people with COVID-19. A small number of people had stroke during admission, most of which occurred late in the course of COVID-19. Previous studies reported similar incidence of acute ischemic stroke or hemorrhagic stroke in COVID-19^{3–5} and in people in ICUs.²⁴ Incidental findings on brain CT identified 3 people on sedatives with stroke, which are more difficult to identify clinically. These results highlight the usefulness of CT, as they led to management changes in many of those scanned. Brain CT may be particularly useful given the high prevalence of critical comorbidities such as coagulopathy, venous thromboembolism, and cardiac arrhythmia in people with critical COVID-19,^{25–27} which all increase the chance of stroke. It also lessens the risk of viral exposure for staff if carried out simultaneously with routine chest CT.

Our results also highlight the importance of a multidisciplinary approach in treating cerebrovascular accidents in people with COVID-19, in whom frequent reassessments may lead to better management. Brain CT and bedside screening tools, which can detect such events, are key for this purpose, especially for people who are unconscious, have a stroke history, or are on mechanical ventilation. Larger cohorts are warranted to quantify the true prevalence and etiology of cerebrovascular accidents in COVID-19 to optimize their treatment.

We did not find evidence that neurologic impairments were directly caused by the virus. SARS-CoV-2 identification was negative in the CSF of all cases tested and systemic condition explained most of them. For those with neurologic complications, the incidence of altered consciousness was not significantly increased compared to other respiratory illness such as chronic obstructive pulmonary disease or asthma.²⁸ Delirium and strokes are often seen in ICUs.^{4,24} Likewise, mild symptoms such as tics, tremor, or muscle cramps are more likely attributable to acute stress disorder and hypocalcemia rather than a direct effect of the virus. There have been reports of mostly nonspecific neurologic symptoms in COVID-19, including

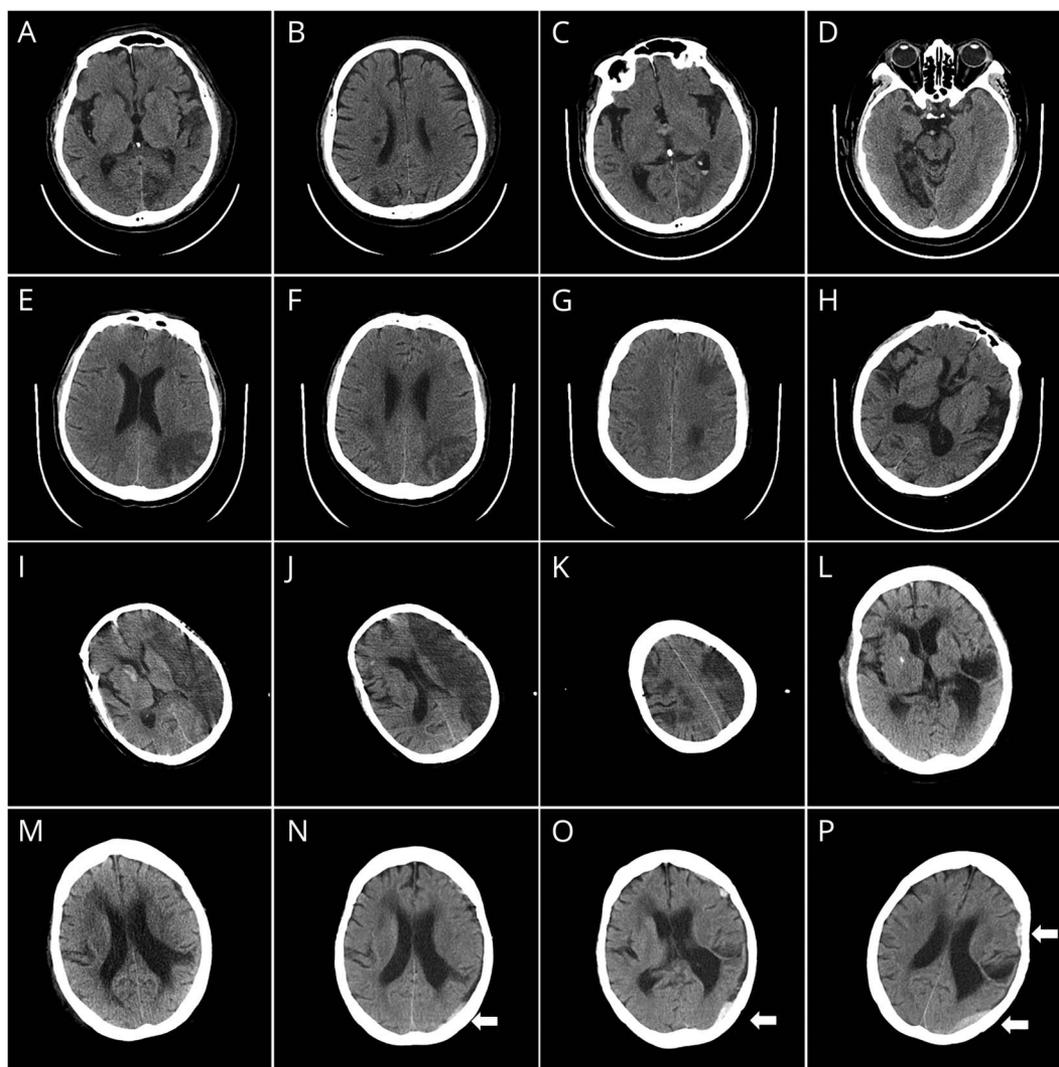
headache, dizziness, and myalgia.^{1,2} There also have been reports of a wide clinical spectrum of more severe symptoms such as acute stroke, acute myelitis, pneumonia complicated by tuberculous meningitis, rhabdomyolysis, Guillain-Barré syndrome, Miller Fisher syndrome, polyneuritis cranialis, and acute hemorrhagic necrotizing encephalopathy.^{3–12} The prevalence of such cases and a causal relationship with the virus is unknown.

We have not identified any individual with epilepsy but they could have been missed in view of our methodology. We did not observe seizures of any type in this cohort, particularly symptomatic seizure or cases of status epilepticus.¹⁷ This was surprising as some individuals had clear risk factors for this type of complication.

To date, no evidence of direct impairments by SARS-CoV-2, such as confirmation of RNA in the CSF or neurons on autopsy or postmortem study, has been established. Another human coronavirus, SARS-CoV, was found in the brain of an individual with encephalopathy in a postmortem study. Eight others showed that the virus was confined to the hypothalamus and cortex in brain autopsy without neurologic impairment reported.^{14,15} Neurologic symptoms were also reported in 4 people during or after Middle East respiratory syndrome, which is also caused by a human coronavirus.²⁹ The pathogenic role of SARS-CoV-2 in neurologic impairment is unclear and needs more investigation.

The severe neurologic complications we have seen are unlikely directly attributable to the virus but it is important to acknowledge common neurologic complications so physicians can be prepared, especially when there is no access to neurology. Early detection of impaired consciousness and delirium may help treatment escalation. The use of brain CT should be encouraged to identify strokes in those at high risk. Thrombolytics and coagulants should be used cautiously in this population.

Figure 2 CT brain scans of patients with COVID-19 with cerebrovascular accidents



(A, B) Images of patient 1 showing multifocal ischemic stroke in both hemispheres. (C) Image of patient 1 taken 10 days after the images in panels A and B, showing the onset of intraventricular bleeding. (D) Image of patient 8 showing ischemic stroke of right temporal occipital junction and parahippocampal gyrus. (E–G) Images of patient 2 showing multifocal cerebral watershed infarction. (H) Unremarkable image of patient 4, taken 2 days before fatal stroke. (I–K) Scans of patient 3 showing bilateral multifocal stroke, hemorrhagic lesions, and large hemispheric infarction on the left side. (L, M) Scans of patient 9 showing previous lesions of stroke. (N–P) Images of the new-onset subdural hematoma (arrow) in the follow-up scans 4, 11, and 16 days after images in panels L and M.

Four of our cases (patients 6 and 11 and 2 who presented with cerebral herniation and traumatic brain injury) initially manifested typical neurologic symptoms but without typical symptoms of COVID-19. As a detailed travel history was taken and they had investigations including chest CT and virus testing, they were promptly channeled into COVID-19 treatment paths. Clinical staff might have put themselves at risk by continuing to work with them under the assumption that they did not have COVID-19 had they not been tested. Our experience highlights the need to consider the epidemiology of COVID-19 and to implement adequate protective measures even when people are not immediately suspected of having COVID-19.

As well as acute neurologic impairments, one should also be aware of potential long-term sequelae. Neuromusculoskeletal disorders following severe acute respiratory syndrome have been

reported.^{13,30} For those surviving an acute respiratory distress syndrome, with delirium, mechanical ventilation, and prolonged exposure to sedatives or sepsis, a high prevalence of cognitive impairment, which decreases quality of life, could be expected.³¹

Our study has several limitations. First, we enrolled people retrospectively; this is unlikely to have introduced bias as the government covers all costs so most would attend a hospital. Second, we did not include many children, as only some of the participating hospitals could admit children. The numbers of children in our cohort could be underestimated if compared to that in the total population with the infection.³² Children, however, seem to be spared from the most critical symptoms and in a recent study of critically ill children with COVID-19 no neurologic complication was reported.³³ Third, no brain MRI,

CT angiography, magnetic resonance angiography, or EEG was performed because of the risk of viral exposure to staff. Finally, 145 people were still in the hospital at study end, so we were not able to ascertain final outcomes; this may have led to an underestimation of the mortality rate but also of new neurologic events. We do not believe, however, that this would make a major difference.

Despite these limitations, new-onset critical neurologic events were identified in fewer than 5% of people during acute COVID-19 infections and this was highly associated with a poor outcome. Evidence for an acute or direct brain insult by the COVID-19 virus is lacking. Neurologists should work closely with other specialties via a multidisciplinary approach to protect the nervous system from short-term and possible long-term impairments. More work, particularly in large cohorts, is warranted to elucidate the full impact of COVID-19 in the CNS, particularly in the medium and long term.

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Disclosure

The authors report no disclosures relevant to this work. Go to Neurology.org/N for full disclosures.

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Appendix (continued)

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Appendix (continued)

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Josemir W. Sander, MD, PhD, FRCP	UCL Queen Square Institute of Neurology, Queen Square, London, UK	Conceptualization and design of the study, critical interpretation of data and results, manuscript revisions for critical intellectual content
Dong Zhou, MD, PhD	Department of Neurology, West China Hospital of Sichuan University, Chengdu	Conceptualization and design of the study, critical interpretation of data and results, manuscript revisions for critical intellectual content, supervision of the study and guarantor

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