Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

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Summary

Background Concerns regarding potential neurological complications of COVID-19 are being increasingly reported, primarily in small series. Larger studies have been limited by both geography and specialty. Comprehensive characterisation of clinical syndromes is crucial to allow rational selection and evaluation of potential therapies. The aim of this study was to investigate the breadth of complications of COVID-19 across the UK that affected the brain.

Methods During the exponential phase of the pandemic, we developed an online network of secure rapid-response case report notification portals across the spectrum of major UK neuroscience bodies, comprising the Association of British Neurologists (ABN), the British Association of Stroke Physicians (BASP), and the Royal College of Psychiatrists (RCPsych), and representing neurology, stroke, psychiatry, and intensive care. Broad clinical syndromes associated with COVID-19 were classified as a cerebrovascular event (defined as an acute ischaemic, haemorrhagic, or thrombotic vascular event involving the brain parenchyma or subarachnoid space), altered mental status (defined as an acute alteration in personality, behaviour, cognition, or consciousness), peripheral neurology (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle), or other (with free text boxes for those not meeting these syndromic presentations). Physicians were encouraged to report cases prospectively and we permitted recent cases to be notified retrospectively when assigned a confirmed date of admission or initial clinical assessment, allowing identification of cases that occurred before notification portals were available. Data collected were compared with the geographical, demographic, and temporal presentation of overall cases of COVID-19 as reported by UK Government public health bodies.

Findings The ABN portal was launched on April 2, 2020, the BASP portal on April 3, 2020, and the RCPsych portal on April 21, 2020. Data lock for this report was on April 26, 2020. During this period, the platforms received notification of 153 unique cases that met the clinical case definitions by clinicians in the UK, with an exponential growth in reported cases that was similar to overall COVID-19 data from UK Government public health bodies. Median patient age was 71 years (range 23–94; IQR 58–79). Complete clinical datasets were available for 125 (82%) of 153 patients. 77 (62%) of 125 patients presented with a cerebrovascular event, of whom 57 (74%) had an ischaemic stroke, nine (12%) an intracerebral haemorrhage, and one (1%) CNS vasculitis. 39 (31%) of 125 patients presented with altered mental status, comprising nine (23%) patients with unspecified encephalopathy and seven (18%) patients with encephalitis. The remaining 23 (59%) patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist, and 21 (92%) of these were new diagnoses. Ten (43%) of 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and four (17%) had an affective disorder. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years, whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years.

Interpretation To our knowledge, this is the first nationwide, cross-specialty surveillance study of acute neurological and psychiatric complications of COVID-19. Altered mental status was the second most common presentation, comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients. This study provides valuable and timely data that are urgently needed by clinicians, researchers, and funders to inform immediate steps in COVID-19 neuroscience research and health policy.

Funding None.

Introduction

In December, 2019, WHO was notified by clinicians in Wuhan, China, of a novel and severe respiratory virus, later called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19, the disease caused by SARS-CoV-2, was recognised as a substantial global

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Jan 1, 2020, and May 11, 2020, with no language restrictions, using the search terms "COVID-19 or SARS-CoV2" with "neurological or psychiatric" and identified 133 publications and 371 publications, respectively. A focus on publications that reported data for the onset of new neurological or psychiatric diagnoses in hospitalised patients with confirmed or probable COVID-19 identified a more restricted subset of baseline data. From a neurological perspective, these publications included case reports or series (with less than ten patients) of stroke (six publications), encephalitis (five publications), seizures (one publication), cranial neuropathies (two publications), and posterior reversible encephalopathy syndrome (one publication). A larger series of 214 patients from Wuhan reported neurological symptoms in 78 patients. However, many of these symptoms were vague—for example, dizziness or headache—although a subset of 13 patients had a cerebrovascular diagnosis. A study from France reported patients with COVID-19-related acute respiratory distress syndrome, of whom eight had neurological manifestations, including two with strokes. We identified many publications that addressed the mental health effects of COVID-19 on the general population, health-care workers, and those with pre-existing psychiatric diagnoses. However, cases of new-onset psychiatric diagnoses in hospitalised patients with confirmed or probable COVID-19 were limited to a few case reports. In the large Wuhan study, acute psychiatric diagnoses were not described. In the French study, although a dysexecutive syndrome was reported in 14 patients and 26 were described as confused, little information was available with regard to what the psychiatric diagnoses were, and this cohort represented only the severe end of the respiratory spectrum.

Added value of this study

By working across the clinical neuroscience communities of neurology, psychiatry, stroke, and neurointensive care, we identified acute presentations of new-onset complications of COVID-19, reflecting the spectrum of the burden of disease. Ischaemic stroke was common in our cohort of 153 patients (most of whom were confirmed to have COVID-19). We identified a large group of patients with altered mental status, reflecting both neurological and psychiatric diagnoses, such as encephalitis and psychosis. Altered mental status was identified across all age groups, and many younger patients had this presentation.

Implications of all the available evidence

Our work highlights the importance of interdisciplinary work in the clinical neurosciences field in the COVID-19 era. Clinicians should be alert to the possibility of patients with COVID-19 developing these complications and, conversely, of the possibility of COVID-19 in patients presenting with acute neurological and psychiatric syndromes. These findings should direct future research to establish the role of viral neurotropism, host immune responses, and genetic factors in the development of such complications so that clinical management strategies can be developed.

public health emergency and SARS-CoV-2 was declared a pandemic on March 11, 2020. The neurological community were alerted to the high prevalence of anosmia and dysgeusia in early reports.[1,2,3] Some of these early cohorts also featured non-specific neurological symptoms, such as dizziness and headache.[1] However, severe neurological and neuropsychiatric presentations associated with COVID-19 have become increasingly apparent, including a patient with encephalitis in China in whom SARS-CoV-2 was identified in cerebrospinal fluid (CSF),[4] a patient with acute necrotising encephalopathy in Japan,[5] and cases of cerebrovascular disease.[1,6]

During other pandemics of respiratory pathogens, including severe acute respiratory syndrome, Middle East respiratory syndrome, and H1N1 influenza, there were similar reports of patients with neurological complications,[7,8] either during the acute phase, thought to reflect direct viral cytopathy or a para-infectious cytokine storm, or later as a post-infectious, probably cellular immune or antibody-mediated phenomenon, classically manifested as Guillain-Barré syndrome.[9] Additionally, occasional neuropsychiatric and psychiatric presentations have been reported in severe coronavirus infections,[10] although such presentations could reflect broader socioeconomic implications of the pandemic on mental health. These complications are relatively uncommon, but such patients are often the most severely affected, necessitating protracted intensive care admission and often resulting in poor outcomes.[7]

Most published reports on the neurological complications of COVID-19 are limited to individual cases or small case series.[1,4,5] A few studies showed the benefits of identifying patients with neurological complications across centres.[1,11] However, these studies have largely been limited to two or three hospitals and are restricted by both geography and specialty, therefore not assessing the neurological and neuropsychiatric complications of COVID-19 across the clinical spectrum of neurology, stroke or acute medicine, psychiatry, and intensive care.

Consequently, many important questions remain for neurologists and psychiatrists. How common are neurological and psychiatric complications in patients with COVID-19? What proportion of neurological and psychiatric complications affect the CNS versus the peripheral nervous system, and are novel syndromes emerging? And who is most at risk?

The breadth of early clinical presentations has not been represented in the literature, at least in part because

patients could be primarily managed by physicians with various clinical specialties, including neurologists, stroke or acute medical physicians, psychiatrists, or intensive care physicians. More comprehensive and integrated epidemiological characterisation is crucial to understanding the mechanisms that underlie these presentations, without which it will be impossible to rationally select, evaluate, and use appropriate therapies.

We aimed to collate data through a large-scale, national, dynamic, cross-specialty collaborative structure, to both inform best practice management guidelines and to direct research priorities.

Methods

Case notification

During the exponential phase of the pandemic, we developed an online network of secure rapid-response case report notification portals (CoroNerve platforms) comprising the Association of British Neurologists (ABN) Rare Diseases Ascertainment and Recruitment (RaDAR),[12] the British Association of Stroke Physicians (BASP),[13] and the Royal College of Psychiatrists (RCPsych),[14] in collaboration with the British Paediatric Neurology Association (BPNA),[15] the Neuro Anaesthesia and Critical Care Society (who used the ABN portal), the Intensive Care Society, and key stakeholders. Reporting portals for fully anonymised details were hosted on the web platforms of these collaborating professional bodies and via a novel web portal. Members of these professional organisations were emailed weekly to remind them of the surveillance programmes and were invited to notify the central CoroNerve Group at CoroNerve.com of any cases of COVID-19 associated with any of the clinical case definitions that they had seen through these portals.

Because of the clinical demands of the pandemic, we identified minimum clinical datasets that could be completed in under 5 min to reflect the crucial data required to determine the confidence in the diagnosis of COVID-19, demography, geography, and the nature of the clinical syndrome. Physicians were encouraged to report cases prospectively and we also permitted recent cases to be notified retrospectively when assigned a confirmed date of admission or initial clinical assessment, allowing identification of cases that occurred before notification portals were available. Patients were not randomly assigned. Awareness of the study and notification portals was increased through social platforms during the peak of the pandemic, including professional webinars, recorded online presentations, and social media. The ABN portal was launched on April 2, 2020, the BASP portal on April 3, 2020, and the RCPsych portal on April 21, 2020. Data lock for this report was on April 26, 2020. Given the propensity for hospitalisation with COVID-19 for older demographic groups, older patients were defined as those aged 60 years or older and younger patients as those less than 60 years old.

For a full list of participating hospitals and the number of cases they notified see the appendix (pp 2–3).

Evidence of COVID-19

Evidence of SARS-CoV-2 infection was defined as confirmed COVID-19 if PCR of respiratory samples (eg, nasal or throat swab) or CSF was positive for viral RNA or if serology was positive for anti-SARS-CoV-2 IgM or IgG. Cases were defined as probable COVID-19 if a chest radiograph or chest CT was consistent with COVID-19 but PCR and serology were negative or not done. Cases were defined as possible COVID-19 if the disease was suspected on clinical grounds by the notifying clinician but PCR, serology, and chest imaging were negative or not done.

Clinical case definitions

Broad clinical syndromes associated with COVID-19 were classified as a cerebrovascular event (defined as an acute ischaemic, haemorrhagic, or thrombotic vascular event involving the brain parenchyma or subarachnoid space), altered mental status (defined as an acute alteration in personality, behaviour, cognition, or consciousness),[16] peripheral neurology (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle), or other (with free text boxes for those not meeting these syndromic presentations). Data were collected on the specific clinical case definitions within these broad presentations, as follows: a cerebrovascular event (ischaemic stroke, intracerebral or subarachnoid haemorrhage, cerebral venous sinus thrombosis, or cerebral vasculitis); altered mental status (encephalopathy, encephalitis—defined as encephalopathy with evidence of inflammation in the CNS [CSF white cell count >5 cells per µL, protein >0·45 g/dL, or MRI consistent with inflammation], seizures [clinical or electroencephalographic evidence], and neuropsychiatric syndromes notified through psychiatrists or neuropsychiatrists [psychosis, neurocognitive

For more on the **central CoroNerve Group** see www.coronerve.com

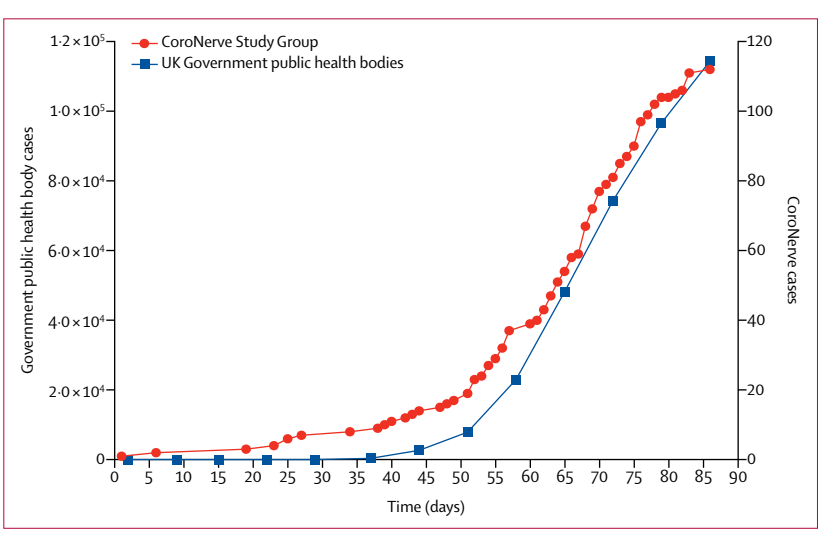

Figure 1: **Temporal distribution of the date of admission or first assessment for cases notified to the CoroNerve Study Group and those identified by UK Government public health bodies**

	All cases (n=153)	Cerebrovascular (n=77)	Altered mental status (n=39)	Peripheral (n=6)	Other (n=3)
Sex at birth					
Male	73 (48%)	44 (57%)	23 (59%)	5 (83%)	1 (33%)
Female	44 (29%)	30 (39%)	14 (36%)	0	0
Not reported	36 (24%)	3 (4%)	2 (5%)	1 (17%)	2 (67%)
Age, years					
≤20	0	0	0	0	0
21–30	4 (3%)	1 (1%)	3 (8%)	0	0
31–40	4 (3%)	1 (1%)	3 (8%)	0	0
41–50	10 (7%)	5 (6%)	4 (10%)	1 (17%)	0
51–60	17 (11%)	6 (8%)	8 (21%)	2 (33%)	1 (33%)
61–70	23 (15%)	16 (21%)	5 (13%)	2 (33%)	0
71–80	31 (20%)	23 (30%)	8 (21%)	0	0
81–90	23 (15%)	18 (23%)	5 (13%)	0	0
≥91	5 (3%)	4 (5%)	1 (3%)	0	0
Missing	36 (24%)	3 (4%)	2 (5%)	1 (17%)	2 (67%)
Median (range; IQR)	71 (23–94; 58–79)	73·5 (25–94; 64–83)	71 (23–91; 48–75)	59 (44–63; 50–62)	54 (54–54)

Data are n (%), unless otherwise indicated.

Table: **Sex and age data for notified patients**

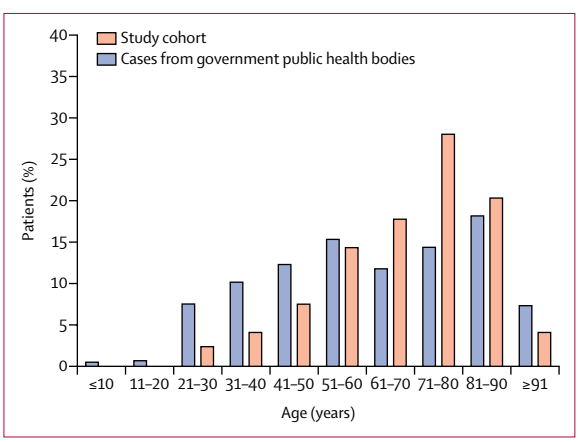

Figure 2: **Age distribution of all cases notified to the CoroNerve Study Group and national data collected by UK Government public health bodies within the first 3 weeks of CoroNerve accepting notifications**

dementia-like syndrome, personality change, catatonia, mania, anxiety or depression, chronic fatigue syndrome, and post-traumatic stress disorder]); and peripheral neurology (Guillain-Barré syndrome, Miller Fisher syndrome, brachial neuritis, myasthenia gravis, peripheral neuropathy, myopathy, myositis—defined as myopathy with evidence of inflammation [eg, by MRI or biopsy of muscle with elevated creatine kinase], and critical illness neuromyopathy).

When patients met more than one specific clinical case definition (eg, seizures and encephalitis), the underlying causal diagnosis was considered primary and complications of that diagnosis considered secondary features (eg, encephalitis would be considered primary and seizures secondary). Where there were discrepancies in classification, these were resolved through discussion with senior authors (BDM, IG, and RHT).

Additional data collection

By asking reporting physicians to submit their contact details at the time of notification (including a National Health Service email address), we established confirmation of the veracity of the data and created a log for subsequent sample collection and longitudinal follow-up studies, through linkage with existing platforms including co-recruitment into the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol, which was also recorded.[17] Data collected were compared with the geographical, demographic, and temporal presentation of overall cases of COVID-19 as reported by national government public health bodies representing each of the regions of the UK (Public Health England, Health Protection Scotland, Public Health Wales, and the Public Health Agency [Northern Ireland]).

The UK Health Research Authority formally confirmed this approach was compliant with regulations regarding anonymised surveillance of routine clinical practice in pandemic conditions, as initiated by the local attending clinician.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the first 3 weeks of the submission portals accepting notifications (April 2–26, 2020), the CoroNerve study platforms received notification of 153 unique cases that met the clinical case definitions by clinicians in the UK. Patients were geographically dispersed across the UK, as were overall laboratory-confirmed cases of patients with COVID-19 reported by government public health bodies during the same time period (appendix p 1). Data from the admitting medical units were available for 152 (99%) of 153 patients. 26 (17%) of 152 patients were from tertiary care hospitals, 125 (82%) were from secondary care hospitals, and one (1%) was from primary care. Overall, 75 (49%) of 153 cases were notified through the BASP portal, 53 (35%) through ABN or CoroNerve.com, and 25 (16%) through the RCPsych portal. Cases were reported retrospectively for 24 (16%) of 153 patients and the remainder were reported prospectively. The BPNA surveillance network was not available for notifications, as the portal was not live during the study period. Data on reporting physician specialty were available for 150 patients: 61 (41%) were stroke physicians, 39 (26%) were neurologists, 26 (17%) were psychiatrists or neuropsychiatrists, 23 (15%) were acute medicine or other physicians, and one (1%) was a general practitioner.

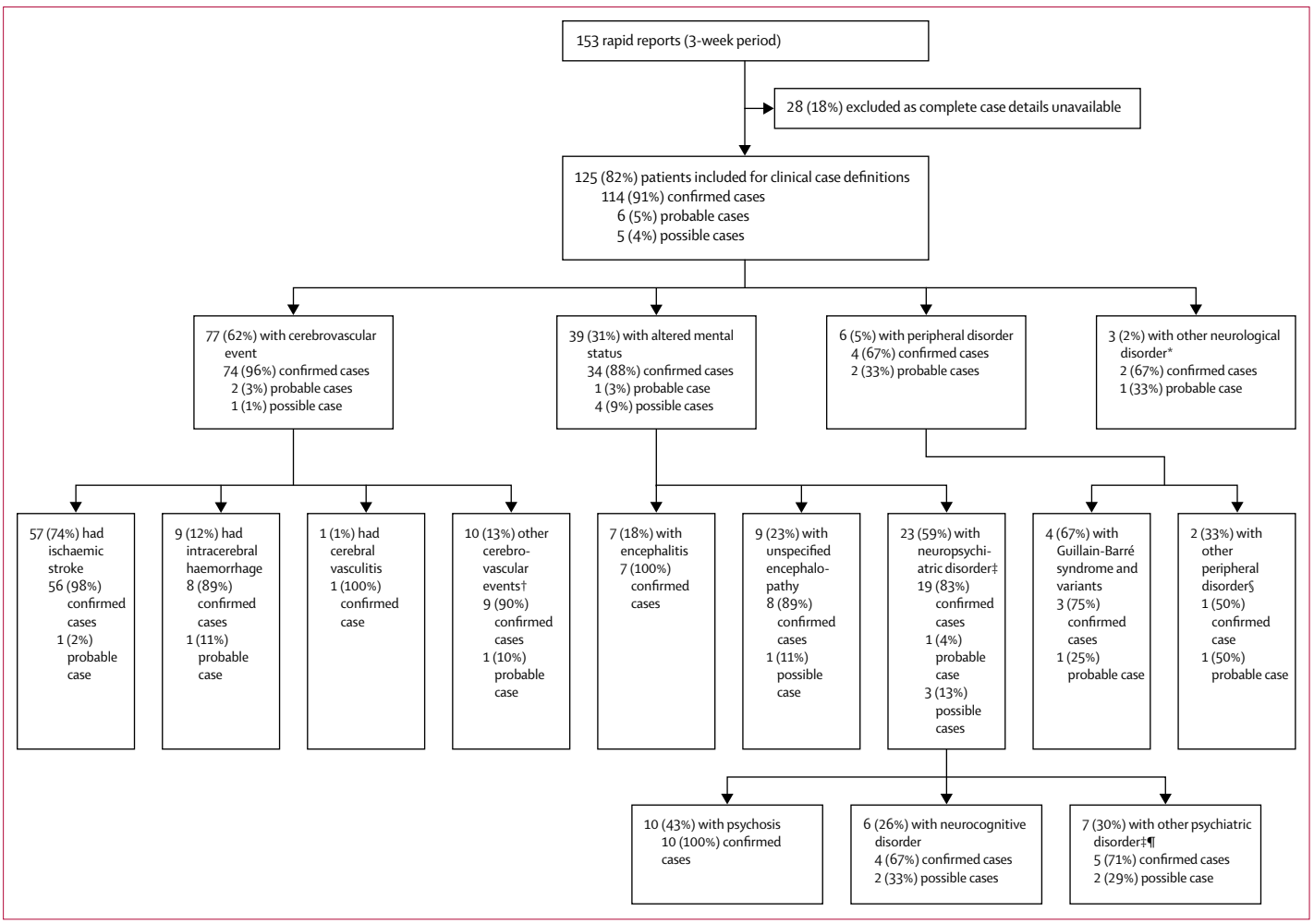

Figure 3: **Number of broad and specific clinical case definitions notified in the dataset, including evidence for severe acute respiratory syndrome coronavirus 2 within each grouping, according to the clinical case definition**

*One patient with opsoclonus-myoclonus syndrome, one patient with sixth nerve palsy, and one patient with seizures. †Two patients with cerebral venous thrombosis, two patients with transient ischaemic attack, one patient with subarachnoid haemorrhage, and five unspecified. ‡1 case with missing SARS-CoV2 data. §One patient with brachial neuritis and one patient with myasthenic crisis. ¶Three patients with depression, two patients with personality change, one patient with catatonia, and one patient with mania.

Complete clinical datasets were available for 125 (82%) of 153 patients. Dates of admission or initial clinical assessment were available for 112 (90%) of 125 patients and correlated with the national case identification data of all laboratory-confirmed patients with COVID-19 reported by government public health bodies over the same time period, reflecting the exponential phase of infection (figure 1).

Data on the sex and age of notified patients are reported in the table. Overall, the median age of 71 years (range 23–94; IQR 58–79) was similar to national data collected through UK Government public health bodies over the same time period, although for some centiles an older population could be overrepresented within the study cohort (figure 2). Data were available for sex for 117 (76%) of 153 patients as this question was not included in the original ABN RaDAR web portal, representing 28 (19%) cases, and this question was not answered in the other portals in eight (5%) cases. Therefore, data regarding sex were available for 117 (94%) of 125 patients for whom these data were requested.

114 (92%) of 125 patients with complete notification data met the criteria for confirmed SARS-CoV-2 infection, five (4%) met the criteria for probable SARS-CoV-2 infection, and five (4%) met the criteria for possible SARS-CoV-2 infection. 77 (62%) of 125 patients presented with the broad clinical syndrome of a cerebrovascular event, of whom 57 (74%) had an ischaemic stroke and nine (12%) an intracerebral haemorrhage. A clinical diagnosis of CNS vasculitis was reported in one (1%) patient with an unusual and otherwise unexplained infarct of the corpus callosum and imaging appearances suggestive of vasculitis; however, the full angiographic report and pathological confirmation were not provided (figure 3). Beyond cerebrovascular events, 39 (31%) of 125 patients presented with altered mental status,

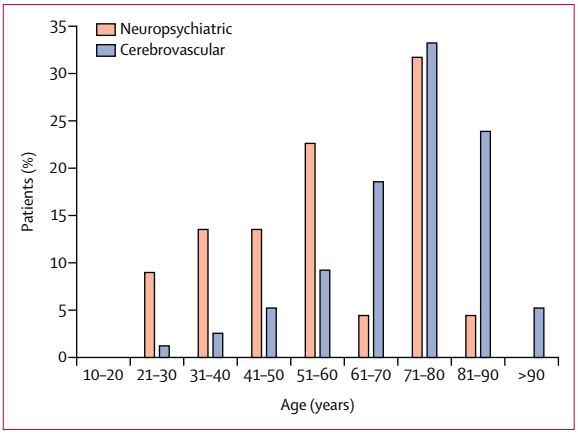

Figure 4: **Age distribution of patients identified through the CoroNerve surveillance study meeting the clinical case definitions for cerebrovascular and neuropsychiatric events**

comprising nine (23%) patients with unspecified encephalopathy and seven (18%) patients with both clinical symptoms or signs of encephalopathy and evidence of CNS inflammation meeting the clinical case definition for encephalitis. All seven patients with encephalitis met the criteria for confirmed SARS-CoV-2 infection. The remaining 23 (59%) patients with altered mental status fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist. Only two (9%) of 23 patients had exacerbations of existing enduring mental illness. Ten (43%) of 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and seven (30%) had an other psychiatric disorder, including one case of catatonia and one case of mania.

Age data were available for 74 (96%) of 77 patients with cerebrovascular events and 37 (95%) of 39 patients with altered mental status. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years, whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years (figure 4).

Discussion

To our knowledge, this is the first systematic, nationwide UK surveillance study of the breadth of acute complications of COVID-19 in the nervous system, undertaken through rapid mobilisation of UK professional bodies representing neurology, stroke or acute medicine, psychiatry, and intensive care. Cases notified by the professional membership of these bodies were obtained from across the UK, and an exponential rise in cases of neurological and psychiatric complications of COVID-19 occurred during the exponential rise in overall COVID-19 cases reported by UK Government public health bodies.

Future studies on neurological complications of COVID-19, particularly those assessing genetic and associated risk factors, would benefit from obtaining notification of all cases of infection admitted to every hospital as a denominator, or a cohort of COVID-19 patients without neurological or psychiatric complications as a control group. However, given the time pressure on busy clinical teams during the pandemic, we focused our notification structure on patients with neurological or psychiatric complications of infection. Cases were reported from physicians who spanned various specialties, and almost all cases met the case definition of confirmed SARS-CoV-2 infection.

Cerebrovascular events in patients with COVID-19, which have been well described elsewhere,[1,9] were also identified as a major group within our cohort. However, we identified a large proportion of cases of acute alteration in mental status, comprising neurological syndromic diagnoses such as encephalopathy and encephalitis and primary psychiatric syndromic diagnoses, such as psychosis. Although cerebrovascular events and altered mental status were identified across all age groups, our cohort confirms that cerebrovascular events predominate in older patients; however, these early data identify that acute alterations in mental status were disproportionately overrepresented in younger patients in our cohort. Our rates of neurological and psychiatric complications of COVID-19 cannot be extrapolated to mildly affected patients or patients with asymptomatic infection, especially those in the community, but give a broad national perspective on complications severe enough to require hospitalisation.

Our approach to case ascertainment has the potential for reporting bias and requires validation through detailed prospective clinicoepidemiological data collection. Plans for such studies should be developed in advance of future pandemics, so that they can be mobilised early during disease spread. A more engaged professional membership or those more used to submitting data to surveillance studies through this approach could potentially be overrepresented in our results. However, this study was the first major national investigation to use a data surveillance approach for clinicians, who notified a large proportion of our cohort (ie, BASP and RCPsych). Additionally, the present study included a priori considerations to determine the strength of the evidence for SARS-CoV-2 infection, and data collection was informed by clear clinical case definitions. Moreover, in this cohort, we conclude that this study is unlikely to have had systematic over ascertainment bias for psychiatric or neuropsychiatric presentations. 41% of cases were reported by stroke physicians, and the RCPsych web portal was launched 18 days later than the other neurological, stroke, and intensive care unit or more general portals, yet we observed a large number of psychiatric or neuropsychiatric notifications. Indeed, as many patients with COVID-19 are managed in intensive care units with sedative and paralytic medications, which can both mask and contribute to iatrogenic complications, our cohort might underrepresent the rate of neurological or

psychiatric symptoms.[18] Since we specifically identified moderate to severe complications of COVID-19 as they were reported for inpatient cases by neurologists and psychiatrists, our cohort might underrepresent patients with milder outpatient symptoms, such as reduced taste or smell. Future hypothesis testing studies building on our findings to infer causal relationships between infection and neurological or neuropsychiatric presentations should adhere to basic principles, such as the criteria for causation outlined by Bradford Hill as they pertain to pandemic respiratory infection and effects on the brain.[19]

Many cerebrovascular events were identified in our study, as reported in previous cohorts and case reports of acute COVID-19 complications.[1,20,21] The pathophysiological mechanisms that underlie cerebrovascular events in COVID-19 require further study, but there is a potential biological rationale for a vasculopathy, with a report of SARS-CoV-2 endothelitis in organs outside the cerebral vasculature[22] and cerebrovascular events,[23] in addition to coagulopathy, along with conventional stroke risk during sepsis.[9,24,25] Comprehensive studies with clear control groups, including patients hospitalised with COVID-19 but without cerebrovascular events and patients with cerebrovascular events but who do not have COVID-19, are required to address this issue.

Confirmation of the link between COVID-19 and new acute psychiatric or neuropsychiatric complications in younger patients will require detailed prospective longitudinal studies. Understanding this association will require systematic participant evaluation, characterisation of immune host responses, exploration of genetic associations, and comparison with appropriate controls (including patients hospitalised with COVID-19 who do not have acute neuropsychiatric features).

Altered mental status is common in patients admitted to hospital with severe infection, especially in those requiring intensive care management. However, this symptom typically predominates in older groups, and might reflect an unmasking of latent neurocognitive degenerative disease or multiple medical comorbidities, often in association with sepsis, hypoxia, and the requirement for polypharmacy and sedative medications. In this study, we observed a disproportionate number of neuropsychiatric presentations in younger patients and a predominance of cerebrovascular complications in older patients, which might reflect the state of health of the cerebral vasculature and associated risk factors, exacerbated by critical illness in older patients.[25] The large number of patients with altered mental status might reflect increased access to neuropsychiatry or psychiatry review for younger patients, and increased attribution of altered mental status to delirium in older patients. Nevertheless, the increased recognition of acute altered mental status in patients hospitalised with COVID-19 warrants study. The exclusion of iatrogenic factors, such as sedatives and antipsychotics, should be quantified in future modelling studies. In our study, although most psychiatric diagnoses were determined as new by the notifying psychiatrist or neuropsychiatrist, we cannot exclude the possibility that these were undiagnosed before the patient developed COVID-19.

Our study population represents a snapshot of hospitalised patients with acute neurological or psychiatric complications associated with COVID-19. Larger, ideally prospective, studies should identify the broader cohort of COVID-19 patients both in and outside hospitals, with capture–recapture analysis and health record linkage to determine clearer estimates of the prevalence of these complications and individuals at risk. Additionally, community studies are required to identify those at risk of both COVID-19 and neurological or psychiatric complications, although this strategy will require widespread serological testing.

The importance of data sharing is increasingly recognised as fundamental to facilitate rapidly responsive clinical research and is particularly crucial during an international emergency, such as the SARS-CoV-2 pandemic. The CoroNerve Study Group has been made possible by open collaboration between several UK institutions. We anticipate added value of sharing data more widely, across European and global partners, particularly in low-income and middle-income countries. The Brain Infections Global COVID-Neuro Network is supporting data collection in such countries through freely available case record forms.[26] Wide collaboration is likely to be even more important for characterising rarer or novel COVID-19-associated neurological syndromes. These enriched populations that reflect less common, but nevertheless severe, disease must be studied in close collaboration with larger surveillance efforts, such as the ISARIC Clinical Characterisation Protocol, to identify at-risk groups, determine the strength of relative risk factors, and have adequate controls for mechanistic studies.

Our nationwide, clinician-reported cohort approach provides valuable and timely information that is urgently needed by clinicians, researchers, and funders to inform the immediate next steps in COVID-19 neuroscience-related research and health policy planning. These national data begin to characterise the spectrum of neurological and neuropsychiatric complications that need to be addressed. This multidisciplinary, coordinated approach should be emulated in detailed national mechanistic studies of COVID-19 and the brain, to distinguish the role of the virus and the host inflammatory response versus the broader socioeconomic effects of the pandemic.[27]

Contributors
AV and BDM drafted the initial manuscript and the document was edited and approved by all coauthors.

Declaration of interests
AV is a Medical Research Council (MRC) PhD fellow. MAE is an Association of British Neurologists PhD fellow. MZ reports personal fees from UCB Pharma outside the submitted work. JPC received funding from the National Institute for Health Research (NIHR) Cambridge

BioMedical Research Centre during the conduct of the study. LAB reports funding from GlaxoSmithKline and Research England, outside the submitted work. AC reports personal fees from independent testimony in court on a range of neuropsychiatric topics and as a paid editor of the Journal of Neurology, Neurosurgery and Psychiatry, outside the submitted work. Additionally, AC is planning a rehabilitation trial after COVID-19, which could produce an application that might be associated with intellectual property. CS has received funding from the MRC, NIHR, The Leducq Foundation, and The Stroke Association. MRT reports grants from Motor Neurone Disease Association and My Name'5 Doddie Foundation, and personal fees from Oxford University Press, Oneworld, Karger Publishing, Orphazyme, BMJ Publishing, and GLG Consulting, outside the submitted work. TS reports consultancy for GlaxoSmithKline Ebola Vaccine programme, Siemens Diagnostics Clinical Advisory Board, Siemens Healthineers Clinical Advisory Board, and the Data Safety Monitoring Committee of the GlaxoSmithKline Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children GSK3390107A (ChAd3 EBO-Z) vaccine, during the conduct of the study. Additionally, TS has a patent filed for a blood test for bacterial meningitis (GB 1606537.7; April 14, 2016). TS is supported by the European Union's Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America Network; 734584). SLP has received funding from the MRC. IG has received funding from the NIHR. RHT reports personal fees from Eisai, GW Pharma, Sanofi, UCB Pharma, Zogenix, Bial, and Arvelle, outside the submitted work. RHT has received funding from the Academy of Medical Sciences (AMS) and Wellcome. BDM has received funding from the MRC, AMS, Wellcome, and the NIHR. BDM and TS are supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (IS-HPU-1112-10117) and the NIHR Global Health Research Group on Brain Infections (17/63/110). All other authors declare no competing interests.

Data sharing

The authors are committed to open science. The broader data from these studies will be made available at the end of the studies wherever possible, within the terms of participant consent and when not otherwise restricted by intellectual property rights or ongoing collaborative research. To avoid the possibility of identifying individual cases, detailed data are not given in the paper or appendix but are available on appropriate request to the corresponding author.

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References

1 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; published online April 10. DOI:10.1001/jamaneurol.2020.1127.

2 Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; published online April 6. DOI:10.1007/s00405-020-05965-1.

3 Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis* 2020; published online March 26. DOI:10.1093/cid/ciaa330.

4 Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020; **94:** 55–58.

5 Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020; published online March 31. DOI:10.1148/radiol.2020201187.

6 Ellul M, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *SSRN* 2020; published online May 7. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3589350 (preprint).

7 Goenka A, Michael BD, Ledger E, et al. Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. *Clin Infect Dis* 2014; **58:** 775–84.

8 Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol* 2017; **13:** 227–33.

9 Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020; **127:** 104362.

10 Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infection: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020; published online May 18. https://doi.org/10.1016/S2215-0366(20)30203-0.

11 Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020; **382:** 2268–70.

12 The Association of British Neurologists. RaDAR. https://www.theabn.org/page/radar (accessed May 4, 2020).

13 The British Association of Stroke Physicians. BASP surveillance for stroke associated with suspected or confirmed COVID-19 infection. https://fitwise.eventsair.com/basp-covid-19-surveillance-project/c-19-stroke-surveillance/Site/Register (accessed May 4, 2020).

14 The Royal College of Psychiatrists. Coronerve surveillance survey. https://www.rcpsych.ac.uk/members/your-faculties/neuropsychiatry/coronerve-surveillance-survey (accessed May 4, 2020).

15 The British Paediatric Neurology Association. Neurological complications of COVID-19. http://www.bpnsu.co.uk/projects/33.php (accessed May 4, 2020).

16 Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 2012; **64:** 347–73.

17 The Global Health Network. The ISARIC Clinical Characterisation Protocol. https://isaric.tghn.org/UK-CCP/ (accessed May 4, 2020).

18 Liu K, Pan M, Xiao Z, Xu X. Neurological manifestations of the coronavirus (SARS-CoV-2) pandemic 2019–2020. *J Neurol Neurosurg Psychiatry* 2020; **91:** 669–70.

19 Ellul MA, Varatharaj A, Nicholson T, et al. Defining causality in COVID-19 and neurological disorders. *J Neurol Neurosurg Psychiatry* 2020; published online June 5. DOI:10.1136/jnnp-2020-323667.

20 Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. *N Engl J Med* 2020; **382:** e60.

21 Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry* 2020; published online April 30. DOI:10.1136/jnnp-2020-323586.

22 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395:** 1417–18.

23 Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *N Engl J Med* 2020; **382:** e38.

24 González-Pinto T, Luna-Rodríguez A, Moreno-Estébanez A, Agirre-Beitia G, Rodríguez-Antigüedad A, Ruiz-Lopez M. Emergency room neurology in times of COVID-19: malignant ischaemic stroke and SARS-CoV-2 infection. *Eur J Neurol* 2020; published online April 30. DOI:10.1111/ene.14286.

25 Boehme AK, Ranawat P, Luna J, Kamel H, Elkind MS. Risk of acute stroke after hospitalization for sepsis: a case-crossover study. *Stroke* 2017; **48:** 574–80.

26 The Global Health Network. Brain Infections Global COVID-Neuro Network. https://braininfectionsglobal.tghn.org/covid-neuro-network/ (May 4, 2020).

27 Holmes EA, O'Connor RC, Perry VH, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry* 2020; **7:** 547–60.