UK-wide surveillance of neurological and neuropsychiatric complications of COVID-19: The first 153 patients


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Summary

Background

Increasingly neurological complications of COVID-19 are identified, mostly in small series. Larger studies have been limited by both geography and specialty. Consequently, the breadth of complications is not represented. Comprehensive characterization of clinical syndromes is critical to rationally select and evaluate potential therapies.

Methods

During the exponential pandemic phase, we developed coordinated online portals for rapid notification across the spectrum of major UK neuroscience bodies, representing neurology, stroke, psychiatry, and intensive care. Evidence of infection and clinical case definitions were applied prospectively. Cases were compared to overall Government Public Health COVID-19 reporting.

Findings

Within three weeks, 153 cases were notified, both geographically and temporally representative of overall COVID-19 Public Health reports. Median (range) age was 71 (23-94) years. 77 (62%) had a cerebrovascular event: 57 (74%) ischemic strokes, nine (12%) intracerebral hemorrhages, and one CNS vasculitis.

The second most common group were 39 (31%) who had altered mental status, including 16 (41%) with encephalopathy of whom seven (44%) had encephalitis. The remaining 23 (59%) had a psychiatric diagnosis of whom 21 (92%) were new diagnoses; including ten (43%) with psychosis, six (26%) neurocognitive (dementia-like) syndrome, and 4 (17%) an affective disorder. Cerebrovascular events predominated in older patients. Conversely, altered mental status, whilst present in all ages, had disproportionate representation in the young.

Interpretation

This is the first nationwide, cross-specialty surveillance study of acute complications of COVID-19 in the nervous system. Alteration in mental status was common, reflecting encephalopathy/encephalitis and primary psychiatric diagnoses, often in young patients.

These data provide valuable and timely information urgently needed by clinicians, researchers, and funders to inform immediate steps in COVID-19 neuroscience research and health policy throughout the areas of neurology and neuropsychiatry.

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Introduction

At the turn of the year the World Health Organization was notified by clinicians in Wuhan, China, of a novel and severe respiratory virus, SARS-CoV-2. Cases of COVID-19 were quickly recognized as a significant global public health emergency and SARS-CoV-2 was declared a pandemic on March 11th, 2020. The neurological community were alerted to the high prevalence of anosmia and dysgeusia in early reports. Some of these early cohorts also featured non-specific neurological symptoms, such as dizziness and headache. However, it became increasingly apparent that severe neurological and neuropsychiatric presentations in association with COVID-19 were occurring; including a case of encephalitis in China in whom SARS-CoV-2 was identified in cerebrospinal fluid (CSF), a case of acute necrotizing encephalopathy in Japan and cerebrovascular disease.

During other pandemics of respiratory pathogens, including SARS, MERS, and H1N1 influenza, there were similar reports of patients with neurological complications. Either during the acute phase, thought to reflect direct viral cytopathy or a para-infectious cytokine storm, or occurring later as a post-infectious, likely cellular immune or antibody-mediated phenomena, classically manifest as Guillain-Barré syndrome. In addition, occasionally neuropsychiatric and psychiatric presentations have been reported in severe coronavirus infections. Whilst the proportion who develop these complications may be relatively rare, these patients are often the most severely affected, necessitating protracted intensive care admission and often resulting in poor outcomes.

Nevertheless, most published reports on neurological complications of COVID-19 are limited to individual cases or small case series. A few studies have demonstrated the benefits of identifying patients across centers, but have largely been limited to 2-3 hospital units and are therefore restricted by both geography and specialty, thereby not assessing the neurological and neuropsychiatric complications of COVID-19 presenting to clinicians across the clinical spectrum of neurology, stroke/acute medicine, psychiatry, and intensive care.

Consequently, many important questions remain for neurologists and neuropsychiatrists. Including: How common are neurological/neuropsychiatric complications in COVID-19 patients? What proportion affect the central versus peripheral nervous system, and are novel syndromes emerging? And who is at risk? This breadth of early clinical presentations has not
been represented, at least in part because patients may be primarily managed by a variety of clinical specialties, including neurologists, stroke or acute medical physicians, psychiatrists, or intensive care physicians. More comprehensive and integrated epidemiological characterization is critical to understanding the mechanisms underlying these presentations, without which it would be impossible to rationally select, evaluate, and use appropriate therapies.

To answer these crucial questions, data need to be collated urgently through large-scale, national, dynamic, cross-specialty collaborative structures, 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 portals comprising the Association of British Neurologists (ABN) Rare Diseases Ascertainment and Recruitment (ABN RaDAR), the British Association of Stroke Physicians (BASP) and the Royal College of Psychiatrists (RCPsych), in collaboration with the British Paediatric Neurology Association (BPNA), the NeuroAnaesthesia and Critical Care Society (NACCS), and key stakeholders. Reporting portals for fully anonymized details were hosted on the web platforms of these collaborating professional bodies and via a novel web portal.

Due to the clinical demands of the pandemic, we identified minimum clinical datasets that could be completed in under 5 minutes, to reflect the critical 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 allowed for recent cases to be notified retrospectively when assigned a confirmed date of admission or initial clinical assessment, to identify cases occurring prior to notification portals being available. The membership of the professional organisations were contacted weekly and invited to notify cases. Awareness 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 the 2nd April, the BASP on the 3rd April, and
Given the propensity for hospitalization with COVID-19 to older demographic groups, older cases were defined as those aged >60 years old and younger cases as those <60 years old.

**Evidence of covid19**

Evidence of SARS-CoV2 infection was defined as ‘Confirmed COVID-19’ if polymerase chain reaction (PCR) of respiratory samples (e.g. nasal/throat swab) or cerebrospinal fluid (CSF) was positive or if serology was positive for anti-SARS-CoV2 IgM/IgG. Cases were defined as ‘Probable’ if a chest radiograph or chest computed tomography (CT) were consistent with COVID-19 but PCR and serology were negative or not performed. Cases were defined as ‘Possible’ if COVID-19 was suspected on clinical grounds by the notifying clinician, but PCR, serology, and chest imaging were negative or not performed.

**Clinical case definitions**

Broad clinical syndromes associated with COVID-19 were classified as ‘Cerebrovascular event’ (defined as an acute ischemic, hemorrhagic, or thrombotic vascular event involving the brain parenchyma or meninges), ‘Altered Mental Status’ (defined as an acute alteration in personality, behavior, cognition, or consciousness),18 ‘Peripheral Neurology’ (defined as involving nerve roots, peripheral nerves, neuromuscular junction, or muscle) , or ‘Other’ (for those not meeting these syndromic presentations). Data were collected on the specific clinical case definitions within these broad presentations, reflecting:

Cerebrovascular event: Ischemic stroke, intracerebral or subarachnoid hemorrhage, 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/µl, protein >0.45g/dL, or MRI consistent with inflammation), seizures (clinical or electroencephalographic evidence), and neuropsychiatric syndromes notified through psychiatrists/neuropsychiatrists: psychosis, neurocognitive (dementia-like syndrome), personality change, catatonia, mania, anxiety/depression, chronic fatigue syndrome, and post-traumatic stress disorder.

Peripheral Neurology: Guillain-Barré syndrome, Miller Fisher syndrome, brachial neuritis, myasthenia gravis, peripheral neuropathy, myopathy, myositis (defined as myopathy with evidence of inflammation e.g. creatine kinase >5 times upper limit of normal), and critical illness neuromyopathy.
When patients met more than one specific syndrome (e.g. seizures and encephalitis) the underlying etiological diagnosis was considered primary and complications of that diagnosis considered secondary features (e.g. encephalitis and seizures respectively). Where there was discrepancy in classification this was resolved through discussion with senior authors (IG, RHT, BDM).

Additional data collection

By asking the reporting physician to submit their contact details at the time of notification (including a National Health Service email address) we established both confirmation of the veracity of the data, and the creation of a log for subsequent sample collection and longitudinal follow-up studies. Data collected were compared relative to the geographic, demographic, and temporal presentation of overall cases of COVID-19 as reported by national Government Public Health bodies representing each of the devolved 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 anonymized surveillance of routine clinical practice in pandemic conditions, as initiated by the local attending clinician. To facilitate future case matching co-recruitment into International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterization Protocol was also recorded.19

Role of the funding source

The funders of the CoroNerve Study Management Group had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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 three weeks of submission portals accepting notifications, the CoroNerve Studies platforms received notification of 153 unique cases meeting the clinical case definitions by clinicians in the UK. The physician contact details for future studies were provided by all who completed the notification. Cases were geographically dispersed across the UK with
comparable distribution to the total laboratory-confirmed cases of patients with COVID-19 reported by Government Public Health bodies (Figure 1). The data of the admitting medical units were available for 152 cases. Of these 26 (17%) were tertiary care hospitals, 125 (82%) were secondary care hospitals, and one was primary care. Overall, 75 (49%) cases were notified through the BASP, 53 (35%) through the ABN/CoroNerve.com, and 25 (16%) through the RCPsych. The BPNA surveillance network was not available for notifications during the first three weeks the other notification portals were live. Data on the reporting physician’s specialty were available for 150 cases and 61 (41%) were stroke physicians, 39 (26%) neurologists, 26 (17%) psychiatrists or neuropsychiatrists, 23 (15%) acute medicine and other physicians, and one General Practitioner.

Complete clinical datasets were available for 125 (82%) cases. The dates of admission or initial clinical assessment were available for 112 (90%) of reported cases and were temporally proportionate to the national case identification data of all laboratory-confirmed patients with COVID-19 reported by Government Public Health bodies over the same time period (Figure 2).

Overall, the median (range) age was 71 (23-94) years, which broadly reflected the national data collected through Government Public Health bodies over the same timeframe, although for some centiles an older population may be over represented (Figure 3). Data on sex was available for 117 (76%) cases and 44 (38%) were female.

Of those with complete notification data, 114 (93%) met the criteria for ‘Confirmed SARS-CoV2 infection’, 5 (4%) for ‘Probable SARS-CoV2 infection’, and 4 (3%) for ‘Possible SARS-CoV2 infection’. Of the whole cohort, 77 (62%) presented with the broad clinical syndrome of a cerebrovascular event, of whom 57 (74%) had suffered an ischemic stroke, nine (12%) an intracerebral hemorrhage, and CNS vasculitis was reported in one case (Figure 4). Beyond cerebrovascular events, 39 (31%) of patients presented with altered mental status, representing 16 (41%) patients with encephalopathy of whom seven (44%) had evidence of CNS inflammation meeting the clinical case definition for encephalitis; all of whom met the criteria for confirmed SARS-CoV2 infection.

Of these cases with altered mental status, 23 (59%) fulfilled the clinical case definitions for psychiatric diagnoses as classified by psychiatrists/neuropsychiatrists. Only two (9%) were exacerbations of existing enduring mental illness, while 21 (92%) were not exacerbations of
long-term psychopathology. Ten (43%) of these cases had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and four (17%) had an affective disorder, after exclusion of known dementia and/or delirium.

Cerebrovascular events were common, and whilst they did occur in the younger population (<60yrs old), there was a marked preponderance in the older age group (>60 years old). Conversely, neuropsychiatric presentations, whilst present in the older group, had disproportionate representation in the younger cohort relative to cerebrovascular disease (Figure 5).

Discussion

Acute complications of COVID-19 are increasingly being recognised, particularly those affecting the CNS. However, most reports reflect series from single institutions or within individual specialties due to the need for timely identification of cases, and as such are open to ascertainment bias.

This is the first systematic, nationwide surveillance study of the breadth of acute complications of COVID-19 in the nervous system, undertaken through rapid mobilization of UK professional bodies reflecting neurology, stroke/acute medicine, psychiatry, and intensive care. Cases notified by the professional membership of these bodies geographically, temporally, and demographically reflected trends in the wider epidemiology of COVID-19, as obtained from national reporting to Government Public Health bodies. Cases were reported from physicians spanning the specialties, and almost all cases met the case definition of confirmed SARS-CoV2 infection. Cerebrovascular events in COVID-19 patients, which are well described elsewhere, were also identified as a major group within our cohort. However, interestingly, a large proportion of cases of acute alteration in mental status were identified reflecting neurological syndromic diagnoses, such as encephalopathy and encephalitis and also primary psychiatric syndromic diagnoses, such as psychosis. Whilst cerebrovascular events and altered mental status were identified across all age groups, our cohort confirms that cerebrovascular events predominate in older patients, but these early data identify that acute alterations in mental status, not attributable to delirium, were disproportionately over represented in younger patients.
This approach to case ascertainment has the potential for reporting bias and requires validation through detailed prospective clinic-epidemiologic data collection. Nevertheless, the present study included a priori considerations to determine the strength of the evidence for SARS-CoV2 infection, and data collection was informed by clear clinical case definitions. In this cohort, surveillance bias is unlikely to have resulted in systematic ascertainment biases for psychiatric/neuropsychiatric presentations. The RCPsych site was launched 18 days later than the other neurological, stroke, ICU/general portals, yet we observed a large number of psychiatric/neuropsychiatric notifications. Although future hypothesis-generating studies building on our findings to infer causal relationships between infection and neurological/neuropsychiatric presentations should adhere to basic principles.21

Despite data notification across the specialties, a large proportion of cerebrovascular events were identified consistent with existing data of acute COVID-19 complications.4,22,23 The pathophysiological mechanisms require further study, but there is a strong biological rationale for a vasculopathy, with reports of direct viral infection of endothelial cells24 and perfusion deficits,25 in addition to coagulopathy; along with conventional stroke risk during sepsis.26-28

Confirmation of the link between COVID-19 and new acute psychiatric/neuropsychiatric complications in younger patients will require detailed prospective longitudinal studies. Understanding this relationship will require comprehensive systematic participant evaluation, characterization of immune and hemostatic host responses, exploration of genetic associations, and comparison with appropriate controls (patients hospitalized with COVID-19 who do not experience acute neuropsychiatric features).

Alteration in mental status is common in patients admitted to hospital with severe infection, especially in those requiring intensive care management. However, this typically predominates in older groups which may reflect an unmasking of latent neurocognitive degenerative disease, and/or multiple medical co-morbidities, often in association with sepsis, hypoxia, and the requirement for sedative medications. In this study we observed a disproportionate number of neuropsychiatric presentations in younger patients, and a predominance of cerebrovascular complications in the older patients, which may reflect the state of health of the cerebral vasculature and associated risk factors, exacerbated by critical illness, in the older cohort.28 The larger number of cases of altered mental status may reflect
increased access to neuropsychiatry/psychiatry review for younger patients, and increased attribution of altered mental status to delirium in the older groups. Nevertheless, that acute alterations in mental status are being increasingly recognised in patients hospitalise with COVID-19 certainly warrants study.

The importance of data sharing is increasingly recognized as fundamental to facilitate rapidly responsive clinical research, and is particularly critical during an international emergency such as that due to SARS-CoV2. The CoroNerve Studies Group has been made possible by open collaboration between several UK institutions. We anticipate there will be added value to sharing data more widely, across European and global partners, particularly those in low and middle-income countries; the Brain Infections Global COVID-Neuro network is supporting data collection in such countries through freely available case record forms. Such wide collaboration is likely to be even more important for characterizing rarer or novel COVID-19-associated neurological syndromes. It is critical that these ‘enriched’ populations reflecting relatively rare, but nevertheless severe, disease are studied in close collaboration with larger surveillance efforts, such as the ISARIC-CCP, to identify at risk groups, determine the strength of relative risk factors, and have adequate controls for mechanistic studies.

In addition, surveillance notification approach such as this, facilitate more focused studies, by retaining the ability to contact individual reporting physicians to revisit selected cases to answer more specific research questions (for example, pertaining to a particular syndrome). Such case identification also provides a framework to secure consent from individual patients for access to additional clinical samples, such as stored serum or CSF obtained for clinical reasons.

This early nation-wide, dynamic, clinician-reported cohort approach provides valuable and timely information urgently needed by clinicians, researchers, and funders to inform the next immediate steps in neuroscience COVID-19-related research and health policy planning. In particular, these national data begin to better characterize the spectrum of neurological and neuropsychiatric complications which need to be addressed.
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Author Statement

BDM, RHT, IG, SP, RK, AV, MAE, and NT form the CoroNerve Study Management Team. AV and BDM drafted the initial manuscript and the revised document was edited and approved by all co-authors.
References


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Figure 1: Geographic distribution of the percentage of neurological and neuropsychiatric case notifications through the CoroNerve platforms (purple) relative to the percentage of overall COVID-19 cases reported by Government Public Health bodies of the UK administrations during the same time frame (blue).
Figure 2. Temporal distribution of the date of admission/first assessment for cases notified to the CoroNerve Studies Group (red) relative to those identified by Government Public Health bodies of the UK administrations (blue).
Figure 3. Age distribution of all cases notified to the CoroNerve studies surveillance programme (red) relative to national data collected by Government Public Health bodies of the UK administrations (blue) within the first 3 weeks of CoroNerve accepting notifications.
Figure 4: Number (percentage) of broad and specific clinical case definitions notified in the dataset, including evidence for SARS-CoV2 within each grouping, according to the clinical case definition (Format: ‘Confirmed/Probable/Possible’).
Figure 5. Age distribution of patients identified through the CoroNerve surveillance study meeting the clinical case definitions for cerebrovascular events (blue) and altered mental status (red).