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Ng Kee Kwong, Koy Chong; Mehta, Puja R; Shukla, Garima; Mehta, Arpan R

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Review article

COVID-19, SARS and MERS: A neurological perspective

Koy Chong Ng Kee Kwong [a], Puja R. Mehta [b], Garima Shukla [c], Arpan R. Mehta [a,d,e,f,g,*]

[a] Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[b] The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK
[c] Division of Neurology, Department of Medicine, Queen's University, Kingston, Ontario, Canada
[d] UK Dementia Research Institute at University of Edinburgh, Edinburgh, UK
[e] Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK
[f] Euan MacDonald Centre, University of Edinburgh, Edinburgh, UK
[g] Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

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ABSTRACT

Central to COVID-19 pathophysiology is an acute respiratory infection primarily manifesting as pneumonia. Two months into the COVID-19 outbreak, however, a retrospective study in China involving more than 200 participants revealed a neurological component to COVID-19 in a subset of patients. The observed symptoms, the cause of which remains unclear, included impaired consciousness, skeletal muscle injury and acute cerebrovascular disease, and appeared more frequently in severe disease. Since then, findings from several studies have hinted at various possible neurological outcomes in COVID-19 patients. Here, we review the historical association between neurological complications and highly pathological coronaviruses including SARS-CoV, MERS-CoV and SARS-CoV-2. We draw from evidence derived from past coronavirus outbreaks, noting the similarities and differences between SARS and MERS, and the current COVID-19 pandemic. We end by briefly discussing possible mechanisms by which the coronavirus impacts on the human nervous system, as well as neurology-specific considerations that arise from the repercussions of COVID-19.

1. Introduction

Officially declared as a global pandemic by the World Health Organisation (WHO) on 11 March 2020, the COVID-19 (Coronavirus Disease 19) outbreak has evolved at an unprecedented rate. Following its emergence in Wuhan, the capital of the Hubei province, People's Republic of China, in December 2019, the total number of confirmed coronavirus cases worldwide has already surpassed 2,900,000 as of 28 April 2020 [1], with actual figures believed to be even higher. The virus responsible for the COVID-19 pandemic, initially designated as "2019-nCoV" (2019 novel coronavirus), was later renamed to "SARS-CoV-2" (severe acute respiratory syndrome coronavirus 2), given its similarity to the previous SARS-CoV.

Whilst numerous comparisons can be drawn between SARS-CoV-2 and its predecessors – SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) – responsible for the SARS and MERS epidemics, respectively, SARS-CoV-2 has unquestionably proved to be the most deadly. The reported COVID-19 global death toll has now risen to more than 200,000 since its first death in early January, far surpassing the combined reported death toll of SARS and MERS, which stands at less than 2,000 [2,3]. Moreover, a considerable number of deaths from COVID-19 are taking place in the community and in care homes, which are commonly not being included in publicised national death tolls. The reported number of COVID-19 cases and deaths in the People's Republic of China has largely been exceeded by those residing elsewhere, with the USA and Europe now the new epicentres of this global health pandemic.

Abbreviations: 2019-nCoV, 2019 novel coronavirus; ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CNS, central nervous system; COVID-19, Coronavirus Disease 19; CRP, C-reactive protein; CSF, cerebrospinal fluid; DPP4, dipeptidyl peptidase 4; MERS-CoV, Middle East respiratory syndrome coronavirus; PNS, peripheral nervous system; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organisation.

* Corresponding author at: Anne Rowling Regenerative Neurology Clinic, Edinburgh Bioquarter, 49 Little France Crescent, Edinburgh EH16 4SB, UK.
E-mail address: amehta@exseed.ed.ac.uk (A.R. Mehta).

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2. Coronavirus: Origin and transmission

Coronaviruses, named after their characteristic crown-shaped microscopic appearance, are positive-sense single-stranded RNA viruses [4]. Taxonomically, they form part of the *Coronavirinae* subfamily *(Coronaviridae* family and *Nidovirales* order). The *Coronavirinae* subfamily consists of four genera, of which betacoronaviruses include many of the most highly pathogenic coronaviruses known to man, including SARS-CoV, MERS-CoV and SARS-CoV-2. Similar to betacoronaviruses, alphacoronaviruses also infect humans and other mammals. The two other genera, gammacoronaviruses and deltacoronaviruses, are more commonly associated with birds.

Whilst the transmission of SARS-CoV and MERS-CoV has been attributed to market civets and dromedary camels, respectively, SARS-CoV-2 apparently emerged from the wet animal market in Wuhan. All three diseases are, however, believed to originate from bats, although this has been difficult to prove [4]. Human-to-human transmission has also not been fully explained, with droplet transmission being most likely, and other mechanisms of spread including fomite and airborne transmission also implicated [5]. Asymptomatic COVID-19 carriers and those with mild symptoms are thought to contribute to the massive transmission potential of COVID-19.

3. Typical clinical presentation

COVID-19, SARS and MERS primarily manifest as respiratory illnesses, which are occasionally accompanied by gastrointestinal manifestations [6]. Disease severity can range from an illness with only mild respiratory symptoms to severe acute respiratory distress syndrome (ARDS). Incubation time is also variable, with symptoms taking from two days to as long as around two weeks to appear [7]. COVID-19 presents most frequently as a pneumonia, with its associated signs and symptoms, including fever, dry cough, and breathlessness, with characteristic radiological changes of bilateral lung opacities [6]. Whilst many of these also feature in SARS and MERS, COVID-19 has a propensity to cause lower respiratory tract infections, as suggested by the relatively less frequent occurrence of symptoms such as rhinorrhoea and sore throat. SARS and MERS are also more commonly linked to gastrointestinal symptoms, including diarrhoea. Furthermore, it has become increasingly clear that all of these highly pathogenic coronaviruses affect the cardiovascular system, with evidence of both acute and chronic cardiovascular features [8].

4. The neurological complications of COVID-19, SARS and MERS

Recent evidence suggests that COVID-19 pathophysiology may also involve the nervous system. A retrospective study in China involving more than 200 participants revealed that a subset of COVID-19 patients experienced neurological symptoms [9]. These included impaired consciousness, acute cerebrovascular disease and skeletal muscle symptoms, suggesting the involvement of both the central nervous system (CNS) and peripheral nervous system (PNS). The observed symptoms were more likely to be present in patients suffering from severe disease. Other possible PNS symptoms included hypogeusia and hyposmia. The link between these neurological symptoms and patient outcome could not be investigated, since patients were still acutely hospitalised at the time of the publication. Another study by the same group reported that in 13 patients COVID-19 infection was followed by acute cerebrovascular disease, including ischaemic stroke, cerebral venous sinus thrombosis and cerebral haemorrhage [10]. These features were again more common in severe disease and older patients.

Consistent with the findings from China, neurological manifestations were also reported by a second study in France, which followed 58 COVID-19 patients admitted to hospital owing to acute respiratory distress syndrome [11]. 84% experienced neurological symptoms at various timepoints, from ICU admission to discontinuation of neuromuscular blockade. The neurological features included evidence of encephalopathy, corticospinal tract dysfunction, agitation and delirium. MRI and perfusion brain imaging conducted in a small subset of patients also revealed leptomeningeal enhancement and bilateral frontotemporal hypoperfusion, and two patients also had evidence of a small acute ischaemic stroke. As we await additional studies to further characterise the associated neurological manifestations of COVID-19, an increasing number of individual case reports have emerged, describing acute neurological disorders ranging from Guillain-Barré syndrome and acute myelitis to acute haemorrhagic necrotising encephalopathy in patients with COVID-19 [12–18].

Whilst relatively fewer neurological associations have been made during past coronavirus epidemics, a number of case reports of SARS patients have documented the development of seizures, myopathy and rhabdomyolysis [19–23]. In one study involving 206 SARS patients, five cases of acute cerebrovascular disease were reported [24]. Whether this merits a parallel being drawn between SARS and COVID-19 pathophysiology is, however, debatable. Noting that these are rare presentations, and acknowledging that they are, in some cases, associated with a differential diagnosis, the presence of viral RNA, in both cerebrospinal fluid (CSF) [19,21] as well as in autopsied brain tissue [23], nevertheless points to a neurotropic component to the SARS coronavirus.

Neurological disorders have also been reported during the MERS outbreak, with neuropathy, delirium and acute cerebrovascular disease being described by several case reports [25–27]. Another study involving 70 MERS patients further reported confusion and seizures in 18 and 6 of the participants, respectively [28], although interpreting such findings again warrants caution. In contrast to SARS, little evidence currently exists for the presence of the MERS coronavirus in CSF. This also appears to be the case for COVID-19, where evidence for viral presence in CSF is still limited to a single case report [15], with other studies unable to replicate these findings thus far [11,12,18].

5. ACE2 receptor

Whilst MERS-CoV infects cells by binding to the dipeptidyl peptidase 4 (DPP4) receptor, SARS-CoV instead acts via the angiotensin-converting enzyme 2 (ACE2) receptor [4]. ACE2, which is a membrane-bound protein expressed across different organs, including skeletal muscle and the brain [29,30], has also recently been found to be the functional receptor of SARS-CoV-2 [31]. Similar to SARS-CoV, SARS-CoV-2 attaches to the host cell membrane through interaction between a spike protein and the host ACE2 receptor [32,33]. Notably, the binding affinity of the SARS-CoV-2 spike protein to ACE2 has been found to be significantly higher than that of the SARS-CoV spike protein [32], although the implications of this remain to be established. Whilst still controversial, ACE inhibitors and ibuprofen may increase ACE2 levels [34], potentially facilitating COVID-19 infection, and are of interest because of their use in the management of migraine.

6. Neurotropism

It is also currently unclear how SARS-CoV-2 invades the human CNS. One suggested mechanism is through haematogenous dissemination, whereby the virus crosses into the CNS from the bloodstream by infecting endothelial cells or leukocytes [35].

Another possible pathway is via retrograde neuronal routes, in which the virus gains access to the CNS by infecting peripheral neurons [35]. Animal studies have demonstrated that SARS-CoV could reach the brain via an olfactory route, promoting neurodegeneration [33]. Emerging evidence from two studies, both available via *bioRxiv* preprint, and therefore yet to be peer-reviewed, suggests that SARS-CoV-2 also gains access to the CNS via the olfactory pathway, with concordant results demonstrating the expression of both the ACE2 receptor and the spike protein protease TMPRSS2, which is also required for SARS-CoV-2 entry, by specific subsets of cells present in the olfactory region [36,37]. Whilst reports of SARS-related olfactory neuropathy are sparse [38], anosmia and hyposmia are increasingly being recognised as key features of COVID-19 infection, often as a presenting symptom [9,39–43]. Thus, these studies could potentially provide promising avenues for future research aimed at improving our understanding of SARS-CoV-2 neurotropism.

7. Potential mechanisms of neurological manifestations of COVID-19

Although various lines of evidence support the involvement of the human nervous system in SARS, MERS and COVID-19, it remains difficult to ascertain how the different neurological features relate to the overall pathophysiology—namely, whether they result directly or indirectly from viral infection, or arise through other mechanisms, such as hypoxia, sepsis or multi-organ failure.

One possible mechanism is via an immune-related pathway. COVID-19 appears to possess an important immune component, with several studies reporting findings such as lymphopenia and raised C-reactive protein (CRP) levels in COVID-19 patients [6,44,45]. Cytokine storm syndromes, including secondary haemophagocytic lymphohistiocytosis (sHLH), have recently gained considerable attention as an uncommon, but fatal, complication of COVID-19 patients, particularly in those with severe disease [46]. Hence, patients with severe COVID-19 are increasingly being monitored for raised ferritin levels, suggestive of hyperinflammation.

Notably, one study reported lower lymphocyte levels and platelet counts in COVID-19 patients presenting with CNS symptoms compared to those without CNS involvement [9,10]. Patients with severe disease were also found to possess higher levels of D-dimer, a marker of a hypercoagulable state and of endogenous fibrinolysis, which could possibly explain why acute cerebrovascular disease more commonly develops in such patients [9,10]. It has therefore been suggested that anti-inflammatory pathways could potentially be targeted early on, aiming to reduce the risk of acute cerebrovascular disease [10].

8. Neurology-specific considerations

There are a number of specific patient management and service delivery considerations that are worth touching on [47–50]. The COVID-19 pandemic has stimulated the rapid dissemination of authoritative and practical information by representative neurology bodies globally, providing, for instance, consensus guidance advising about isolation strategies for high-risk patients, and the management considerations for patients on immunosuppressive agents. The scope of these guidelines will change based on emerging data from our colleagues in other specialties, such as whether thromboprophylaxis regimes, or the process of taking informed consent need to be altered in patients requiring intravenous immunoglobulin therapy, given the concerns about prothrombotic states in COVID-19. Moreover, given the possibility that a significant driver of pathology may be related to an overactive immune state, it remains an open question whether certain immunosuppressive agents may be beneficial, such as has been suggested in a case report of ocrelizumab in multiple sclerosis [51]. Owing to outpatient departments being closed to mitigate COVID-19 transmission, several academic centres, hospitals and clinics have rapidly adopted new strategies for managing neurology patients, and it is heartening to see those neurological centres lacking in infrastructure for tele-medicine catching up with those that did, in a concerted effort to maintain acute neurology and outpatient services.

9. Concluding remarks

The neurology of COVID-19 and other coronavirus-related infections is a rapidly evolving area of medicine. Whilst most studies in the past, including those relating to SARS and MERS, have mainly involved small patient samples, the latest evidence on COVID-19 suggests that neurological events may occur in a significant proportion of patients. Further studies will allow for an assessment of the presence of any long-term neurological sequelae. There is a need for record-linkage studies that can establish varying degrees of associations between the incidence, severity and prognosis of COVID-19, and specific immunosuppressive disease modifying therapies, that would help in risk stratification and risk modification exercises for the management of patients with neuroinflammatory disorders; this would be especially useful if there were a second wave of COVID-19 illness. Finally, improving our understanding of the neurobiology of coronaviruses could augment our knowledge of neurological disorders with potential viral associations, such as viral encephalitis and multiple sclerosis.

Author contributions

K.C.N.K.K. performed the initial literature review and wrote the first draft of the manuscript. A.R.M. supervised the work. P.R.M., G. S. and A.R.M. revised subsequent drafts. All authors approved the final version of the manuscript.

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Declaration of Competing Interest

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

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