BRAIN COMMUNICATIONS

The cognitive consequences of the COVID-19 epidemic: collateral damage?

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Recovery from coronavirus disease 2019 (COVID-19) will be principally defined in terms of remission from respiratory symptoms; however, both clinical and animal studies have shown that coronaviruses may spread to the nervous system. A systematic search on previous viral epidemics revealed that while there has been relatively little research in this area, clinical studies have commonly reported neurological disorders and cognitive difficulties. Little is known with regard to their incidence, duration or underlying neural basis. The hippocampus appears to be particularly vulnerable to coronavirus infections, thus increasing the probability of post-infection memory impairment, and acceleration of neurodegenerative disorders such as Alzheimer's disease. Future knowledge of the impact of COVID-19, from epidemiological studies and clinical practice, will be needed to develop future screening and treatment programmes to minimize the long-term cognitive consequences of COVID-19.

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Abbreviations: COVID-19 = coronavirus disease 19; HcoV = human coronaviruses; MERS-CoV = Middle East respiratory syndrome; SARS-CoV = severe acute respiratory syndrome

The majority of persons suffering from COVID-19 will recover; recovery being principally defined in terms of remission of respiratory tract symptoms. But is this the end of the story for these patients? There is increasing evidence that coronaviruses spread to extra-respiratory organs, notably the central nervous system (CNS) (Desforges *et al.*, 2014, 2019; Bohmwald *et al.*, 2018); however, little is currently known about the longer-term effects on the brain of coronavirus infection and its consequences in terms of cognitive functioning. The scarcity of research in this area precludes formal meta-analysis, yet a number of observations from a systematic literature search suggest this to be potentially an important question for both clinical research and post-infection patient management. A literature search was undertaken from 2000 to ensure coverage of the principal recent coronavirus epidemics using Medline, SCOPUS and Google Scholar databases.

Neurological symptoms and sub-clinical cognitive dysfunction in the aftermath of COVID-19 infection are likely to result from multiple and interacting causes, notably direct damage by the virus to the cortex and adjacent subcortical structures, indirect effects due to non-CNS systemic impairment and psychological trauma.

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Virus-induced CNS damage

Human coronaviruses (HcoV) are one of several virus groups which are considered to be potentially neurotrophic. It has been observed from previous epidemics that the respiratory coronaviruses may penetrate into the brain and cerebrospinal fluid, permeating the CNS in less than a week, and subsequently observable in cerebrospinal fluid (Bohmwald *et al.*, 2018). An autopsy series of severe acute respiratory syndrome (SARS-CoV) victims following the 2003 epidemic revealed SARS-CoV genome sequences throughout the cortex and hypothalamus (Gu *et al.*, 2005). In patients infected by Middle East respiratory syndrome (MERS-CoV), diffuse lesions were identified in several brain regions, including white matter and the subcortical areas of the frontal, temporal and parietal lobes (Arabi *et al.*, 2015). Two principal mechanisms of CNS invasion have been proposed:

i. The blood–brain barrier, the first line of defense against viral infection, is composed in part of cerebral microvascular endothelium cells between which there are tight junctions controlling barrier permeability which appear to be compromised in the course of coronavirus infection, for example by inflammation (Koyuncu *et al.*, 2013; Miner and Diamond 2016).
ii. The virus may directly infect neurons in the periphery or olfactory sensory neurones and thus use axonal transport to gain access to the CNS (Dahm *et al.*, 2016).

Coronaviruses produce a wide variety of acute CNS symptoms including headaches, epileptic seizures, cognitive dysfunction, motor difficulties and loss of consciousness, and may also contribute to respiratory difficulties through invasion of the brain stem and via a synapse-connected route to the medullary cardiorespiratory centre (Arabi *et al.*, 2015; Bohmwald *et al.*, 2018; Gandhi *et al.*, 2020; Li *et al.*, 2020). Although no clear aetiological pathway has been established between infection and human neurological diseases, the neuropathogenicity of HCoV is being increasingly recognized in humans, with several recent reports associating positive cases with multiple neurological disorders including encephalitis (Morfopoulou *et al.*, 2016), and Guillain–Barré syndrome (Sharma *et al.*, 2019). Other strains of coronavirus (e.g. 229E) have also been found in the brains of patients with Multiple Sclerosis (Arbour *et al.*, 2000). The presence and persistence of HCoV in human brains also appears to aggravate chronic neurological disorders such as Parkinson's disease (Fazzini *et al.*, 1992). Already several clinical observations have been published regarding the neurological consequences of the current COVID-19 epidemic, including reports of loss of speech and comprehension, encephalopathy (Filatov *et al.*, 2020) and Guillain–Barre syndrome (Zhao *et al.*, 2020).

While HCoV infection appears to spread rapidly throughout the CNS, the temporal region appears to be a consistent focus. Animal studies point more specifically to the vulnerability of the hippocampus with greater neuronal loss in CA1 and CA3 (Jacomy *et al.*, 2006) which would be predicted to have a detrimental effect on both learning and spatial orientation. The specific vulnerability of the hippocampus to respiratory virus infection has been previously observed in non-coronavirus infections. Studies of mice infected with influenza virus (Hosseini *et al.*, 2018) found changes in both hippocampal morphology and function, with short-term deterioration in hippocampus-dependent learning and reduced long-term potentiation associated with impairment in spatial memory. To date comprehensive neuropsychological assessment of patients, which would include tests of whole hippocampal function (such as tests of delayed recall or spatial memory) as well as novel tests probing hippocampal sub-regions such as tests of spatial memory which may aid detection of CA1 damage (Bartsch *et al.*, 2010) and a pattern completion task assessing CA3 function (Gold and Kesner 2005; Grande *et al.*, 2019), has not been carried out in relation to HCoV.

If hippocampal damage is indeed a consequence of HCoV infection then the question is raised as to whether this may lead to acceleration of hippocampal-related degeneration as occurs in Alzheimer's disease and hasten disease onset in previously asymptomatic individuals. Animal studies have indicated that inflammation related to viral infection significantly worsens Alzheimer's disease-related tau pathology and results in impairment of spatial memory (Sy *et al.*, 2011), now considered to be one of the first cognitive features of Alzheimer's disease.

Cognitive dysfunction due to non-CNS systemic impairment

Although numerous body organs are affected by coronaviruses, the respiratory system is the most severely compromised. A small study has recently estimated that 70% of critically ill patients admitted to intensive care with COVID-19 require mechanical ventilation (Arentz *et al.*, 2020), all of whom developed acute respiratory distress syndrome within 3 days. Previous neuropsychological studies of long-term outcomes for adults requiring ventilation for multiple causes observed impairments in attention, memory, verbal fluency, processing speed and executive functioning in 78% of patients 1 year after discharge and around half of patients up to 2 years (Hopkins *et al.*, 1999, 2005; Mikkelsen *et al.*, 2012). Adhikari *et al.* (2011) observed self-reported memory problems persisting up to 5 years after acute respiratory distress syndrome and impacting significantly on everyday functioning, notably taking medication and keeping medical appointments. While anxiety, depression and post-traumatic stress syndrome are also common in acute

respiratory distress syndrome patients, and may contribute to cognitive impairment (Adhikari *et al.*, 2011), there is some evidence to suggest that cognitive deficits occur independently of psychological problems, and are associated with severity of infection (Mikkelsen *et al.*, 2012).

Hypoxia, a common cause of neuropsychological changes observed in acute respiratory distress syndrome, has been associated with cerebral atrophy and ventricular enlargement (Hopkins *et al.*, 2006), with duration of hypoxia correlating with attention, verbal memory and executive functioning scores at discharge (Hopkins *et al.*, 2005). However, acute respiratory distress syndrome may also involve inflammatory responses (Han and Mallampalli, 2015) as well as anaemia and ischaemia, leading to cardiovascular and liver failure (Matthay and Zemans, 2011). Such a cascade of neurological and physiological events may further exacerbate neurological injury in acute stages to promote chronic cognitive dysfunction.

Cognitive difficulties related to psychological distress

Cognitive difficulties are symptomatic features of all mental disorders. High rates of psychological symptoms, notably anxiety, depression, suicidal behaviour and post-traumatic stress syndrome have been reported in the general population following previous HCoV epidemics, irrespective of infectious status (Du *et al.*, 2003; Jeong *et al.*, 2016). A study of patients quarantined for suspected or confirmed MERS-CoV ($n = 40$), estimated that 70.8% of confirmed patients who survived the illness ($n = 24$) exhibited psychiatric symptoms, including hallucinations and psychosis, with 40% receiving a psychiatric diagnosis during their hospital admittance. Interestingly, none of the suspected but unconfirmed MERS-CoV patients exhibited any symptoms (Kim *et al.*, 2018), indicating a possible viral mechanism underlying psychiatric disturbance, a dose-response effect or a greater psychological impact from receiving a confirmed respiratory illness diagnosis. A study of 90 SARS-CoV cases with a 97% response rate similarly showed high levels of psychological distress with 59% diagnosed with psychiatric disorders and a continuing prevalence of 33% at 30 month follow-up. Severity of psychological symptoms was found to be related to severity of illness and functional impairment (Mak *et al.*, 2009; Wing and Leung, 2012).

Thus while higher rates of psychiatric symptoms might be expected in the general population following the epidemic due to exposure to traumatic life events (loss of income, fear, death of friends and relatives), nested within this group may be persons whose cognitive and psychological disorders are directly related to HCoV brain changes. The question might then be raised as to whether the latter group will respond to standard treatment for example with anti-depressants, anxiolytics and cognitive therapies.

The small amount of information available from animal studies and previous respiratory epidemics suggests not only that HCoV may affect the brain, but that the consequent effect on cognitive functioning could potentially persist for a long period following recovery. For infected persons already suffering from CNS disorders the effects are likely to be even more debilitating. While new cases of well-characterized neurological disorders subsequent to the current epidemic may be relatively easy to identify, persisting sub-clinical disorders such as mild cognitive dysfunction, selective memory and speech impairments or exacerbation of pre-existing degenerative neuropathologies such as vascular dementia and Alzheimer's disease, presenting principally in general practice, may easily go undetected or be attributed to psychological reactions to the fear and social upheaval generated by the pandemic.

Conclusion

In the face of increasing reports of CNS involvement in COVID-19 cases, the current epidemic is likely to be accompanied by a significant increase in the prevalence of longer-term cognitive dysfunction impacting on ability to return to everyday functioning. This is likely to be due not only to the behavioural consequences of incident neurological disorders directly related to the virus, but also secondary to damage to other body organs, psychiatric disorders and the worsening of pre-existing cognitive difficulties. The number of persons exposed to the virus likely to be affected and the protective factors operating in cases who do not experience cognitive changes is presently unknown. Studies of cognitive dysfunction related to previous epidemics are few and too small to make estimations at a population level.

Further research is needed to understand (i) the range of COVID-19 associated neurological disorders and their cognitive manifestations; (ii) the underlying associations between viral spread, associated proinflammatory changes and disease pathogenesis; (iii) the duration and extent of neurological and cognitive changes following resolution of the acute viral illness; (iv) the association between severity of the viral illness and subsequent cognitive dysfunction; (v) the effect of antiviral, psychological and other interventions (when available) on short- and long-term cognitive function.

The current coronavirus outbreak is unlikely to be the last (with SARS and MERS, COVID-19 this is the third coronavirus epidemic in 10 years). It is therefore imperative that the medical-scientific community look beyond the current acute crisis to the links between coronavirus infection and long-term neurological sequelae. While basic science research will deliver insights into potential mechanistic relationships between viral infections and neurological disease, better understanding of these associations

may inform treatment plans aimed both at treating the acute infection and limiting downstream cognitive decline. For instance, if future work showed that viral load and/or subsequent proinflammatory state correlated with long-term cognitive outcome then in future outbreaks treatment protocols could mitigate against the latter by adjusting the dose and duration of antiviral therapies or add second stage anti-inflammatory treatments.

This research could be taken forward in several ways. Existing longitudinal studies of neurological disorders could be expanded to include acquisition of data concerning COVID-19 exposure and antibody status into existing research protocols which already capture data on cognitive function, brain imaging and disease biomarkers. Data from large prospective cohorts such as UK Biobank could provide population-scale data with clearer information regarding prevalence and persistence of effects over extensive timelines. In parallel, preclinical studies aimed at uncovering the mechanistic association between coronavirus infection and neurological disease will be facilitated by the recent creation of mouse models of COVID-19, which will enable assessment of the interaction between viral pathology and neurodegeneration and will provide a resource for the development of new treatments (Wang, 2020). These will be complemented by the accumulation of information about disease onset and clinical progression, particularly from general practice, which will be crucially important for the implementation of future population-level screening and treatment programmes.

The scope and severity of the current COVID-19 pandemic are unparalleled in modern society. The downstream implications for neurological function may be equally grave. While the current focus is on acute disease management, in the near future attention will need to turn to the long-term consequences of COVID-19 infection and their mitigation.

Competing interests

The authors report no competing interests.

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