The emergence of cognitive COVID

The scale of the COVID-19 pandemic has impacted health care systems on a global level. As the pandemic moves into its second year, attention is beginning to turn towards the medium- and long-term consequences of the infection. High on the list of priorities is the issue of cognitive impairment, not only as a direct effect of neurotropic viral brain infiltration but also due to indirect factors associated with the pandemic, such as increased social isolation and mental health problems.

While associations between neurotropic respiratory viruses and brain changes have been documented since the 1918 influenza epidemic, the cognitive consequences of these changes have until now received very little attention. The increasing interest in both the spread of coronaviruses to the central nervous system (CNS) and the longer-term clinical presentations of infected individuals has led to a re-evaluation of the importance of cognitive changes.

A meta-analysis[1] of 3,559 adult cases collectively drawn from the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 epidemics identified memory impairment in one third of cases at hospital admission and in 19% of cases post-illness, with the latter notably also affecting younger adults. Initial studies indicate that cognitive dysfunction extends beyond the acute stage, with 33% of COVID-19 cases having a dysexecutive syndrome by the time of discharge from hospital[2]. A study of 18 patients with mild to moderate COVID-19 disease (not requiring intensive care unit admission) and a mean age of 42 years, examined a median of 85 days after recovery, found that over 75% had episodic memory, attention and concentration difficulties which were not associated with fatigue, depression, hospitalization, treatment, viremia or acute inflammation[3]. These initial data indicate that cognitive changes may occur after milder infections and may be attributable to direct brain infiltration rather than to medical comorbidities or stress reactions.

Another early indicator of the prevalence of COVID-19-related cognitive impairment is provided by a UK study of 153 patients, half under age 60, which found that 26% had dementia-like cognitive disorders and a further 17% had affective disorders potentially impacting on cognitive function[4].

In short, there is accumulating evidence that COVID-19 infection is associated with cognitive impairment that extends beyond the acute phase of illness. Given the scale of the pandemic and the implications for both working age adults and the older population at risk of dementia, these emerging data highlight the urgent need to better understand the mechanisms resulting in cognitive dysfunction, with a view to introducing interventions and public health strategies to combat these deleterious longer-term effects of the pandemic.

The effect of SARS-CoV-2 on cognition may relate to the vulnerability of various CNS cells to the virus and to its direct infiltration of the CNS. Viral attachment to host cells results from binding of the S1 subunit of the S protein, one of four structural proteins of the SARS-CoV-2 virion, to the angiotensin-converting enzyme 2 (ACE2) receptor on cell surfaces, with subsequent intracellular entry of the viral genome occurring after fusion of viral and host cell membranes. As such, the cellular tropism of SARS-CoV-2 relates to the expression of the ACE2 receptor[5]. Outside the CNS, the receptor is expressed in alveoli, gut, kidney and epidermis, as well as vascular endothelial cells. Within the CNS, it is expressed in neurons, astrocytes, oligodendrocytes and endothelial cells. Regionally, high concentrations of the ACE2 receptor are found in the olfactory bulb, substantia nigra, middle temporal gyrus, and posterior cingulate gyrus[6].

Two direct mechanisms underpin the neurotropism of SARS-CoV-2 and its access to the CNS: a) retrograde axonal transport following invasion of peripheral olfactory neurons, and b) haematogenous breach of the blood-brain barrier following infection of this barrier or choroid plexus endothelial cells. The pathological effect of this direct viral infiltration is augmented by a brisk immune response and inflammation, with the associated cytokine storm further compromising the blood-brain barrier, and by vasculopathy arising from hypercoagulability, disseminated intravascular coagulation and hypoxaemia.

The resultant clinical manifestations of this CNS pathology are multiple[7]. They include inflammatory disorders (meningoencephalitis, acute disseminated encephalomyelitis), encephalopathies presenting with behavioural disturbances, seizures, and cerebrovascular disease (both thrombotic and haemorrhagic). The prevalence of CNS manifestations in severe infection is high: of 64 patients with acute respiratory distress syndrome, 69% had agitation and 65% had confusion, with a high proportion of those imaged showing magnetic resonance imaging (MRI) changes in the form of altered perfusion, ischaemic stroke and leptomeningeal enhancement[2].

The relative recency of the pandemic means that there are at present only limited data on the impact of COVID-19 infection on cognitive function beyond the acute illness. However, both direct and indirect effects of the infection indicate a likelihood of longer-term cognitive impairment. SARS-CoV-2 invasion of peripheral olfactory neurons, now recognized as one component of the virally-induced acute anosmia, permits trans-synaptic viral spread to cortical regions receiving primary and secondary input from the olfactory tract, notably the entorhinal cortex and the hippocampus. The involvement of these regions in episodic memory and spatial navigation raises the possibility of COVID-19 infection causing longer-term impairment in these cognitive domains. This will be amplified by indirect consequences of the infection in terms of other pathophysiological effects, notably virally-mediated vascular pathology and inflammatory responses, psychological trauma and need for critical care[8]. Preliminary estimates of the prevalence and timescales of such effects can be gleaned from previous neuropsychological studies of long-term post-ventilation outcomes, with cognitive impairment observed in 78% of patients at one year and with persisting memory prob-

lems persisting up to five years in around 50%, independent of psychological problems[9].

Finally, there is the potential risk that COVID-19 infection may cause long-term cognitive decline by accelerating the onset of neurodegenerative dementia. The severity of the infection is greater at higher ages (perhaps due in part to an age-related decline in ACE2 expression), and the neural pathways along which SARS-CoV-2 may be transported overlap with those implicated at the onset of Parkinson's and Alzheimer's disease, such as the cognitively eloquent regions within the medial temporal lobe. This overlap in regional vulnerability may provide the anatomical basis for an interaction between SARS-CoV-2 and neurodegenerative pathology, mirroring the acceleration of beta-amyloid and tau pathology caused by other neurotropic viruses such as HIV and herpes viruses.

Extensive future work will be needed to map out the mechanisms and prevalence of long-term "cognitive COVID". *In vivo* and *in vitro* lab studies can evaluate the interaction of viral and neurodegenerative proteins and any potential synergistic effect on synaptic and neuronal function, while large scale longitudinal epidemiological studies will be required to identify the demographic, genetic and psychosocial risk factors of COVID-19-related cognitive decline, and to differentiate between direct and indirect effects of the infection. Targeted cognitive testing, focusing on the functions of vulnerable brain regions, will help differentiate cognitive dysfunction directly due to the infection from that associated with depression and other mental health issues.

Lessons learned during the first stage of the pandemic have improved acute clinical outcomes. As the second stage unfolds, it is imperative that attention now focus on the implications of COVID-19 infection for long-term cognitive impairment and dementia risk, to aid prospective detection and intervention with pharmacological and public health strategies.

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