THE *LANCET* COVID-19 COMMISSION

TASK FORCE ON MENTAL HEALTH

Early Findings on The Neurological Consequences of COVID-19

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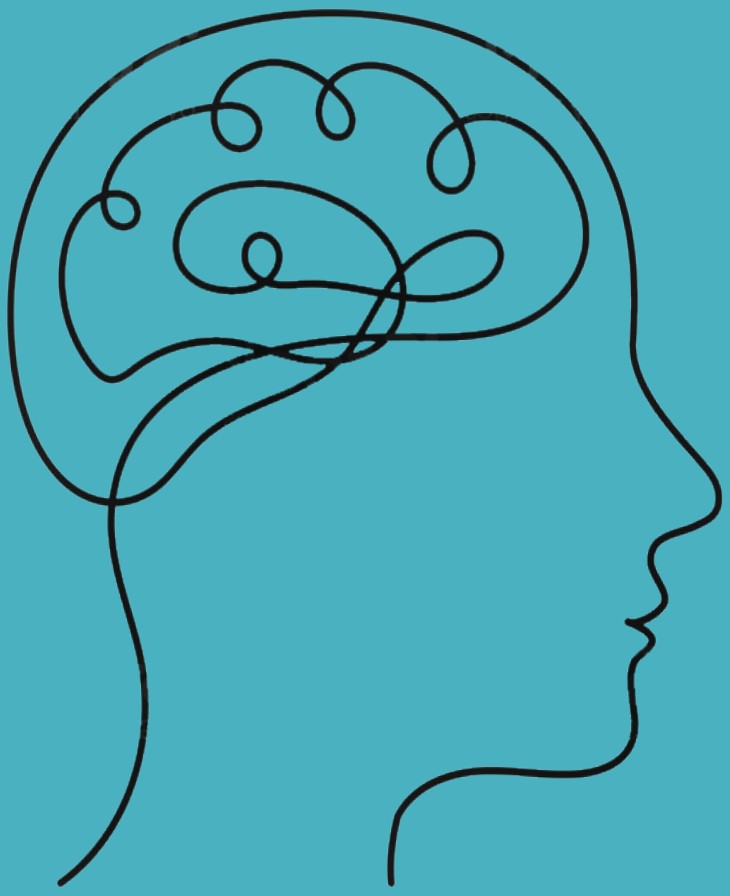

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Task Force on Mental Health

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COVID-19 COMMISSION

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The following report has been posted online by the Commission Secretariat, and has not been peer-reviewed or published in *The Lancet*, nor in any other journal. This reports intends to bring together expert views on key topics as the COVID-19 pandemic unfolds.

EXECUTIVE SUMMARY

- Early evidence suggests that COVID-19 has both mild/moderate (e.g., loss of smell (anosmia), loss of taste (ageusia), latent blinks (heterophila), headaches, dizziness, confusion) and more severe outcomes (e.g., cognitive impairments, seizures, delirium, psychosis, strokes).
- Longer-term neuropsychiatric manifestations may also occur.

Since the first confirmed case in Wuhan, China on December 31, 2019, the novel coronavirus (SARS-CoV-2) has spread quickly, infecting 165 million people as of May 2021. Since this first detection, research has indicated that people contracting the virus may suffer neurological and mental disorders and deficits, in addition to the respiratory and other organ challenges caused by COVID-19. Here, we present a brief summary of the neurological consequences of contracting COVID-19, both during infection and beyond.

NEUROLOGICAL PROBLEMS EXPERIENCED DURING COVID-19 INFECTION

A growing body of evidence suggests that COVID-19 is associated with neurological disorders and deficits.[3,19,20] Some reported neurological symptoms and signs associated with COVID-19 infection are anosmia (loss of smell), ageusia (loss of taste), heterophoria (latent squint)[1], and headaches. Anosmia and ageusia appear quite common. In a sample of 417 patients with mild to moderate COVID-19 symptoms spanning 12 hospitals in Europe, 86% suffered olfactory dysfunction and 89% suffered gustatory dysfunction.[10] Other data collected from 214 individuals in Wuhan, China in January and February 2020 report that anosmia and ageusia may be some of the earliest symptoms, detectable in some individuals before respiratory difficulties emerge.[12] Similar observations are noted in case studies as well (e.g., Zanin et al., 2020). Although olfaction tends to return upon COVID-19 recovery, gustatory deficiencies have been seen to persist beyond respiratory symptoms in over 70% of patients in some samples.[12] A meta-analysis reporting on data from 3,598 cases suggests that headaches are also a common symptom of COVID-19 infection, appearing in 12% of hospitalized patients,[2] and among mild to moderate cases that rarely result in hospitalization.[1,17] A study of 917 people in Wuhan, China from January to March 2020 indicate that these non-specific symptoms can all be caused by the infection, while other neurological conditions may be due to sedation during ventilation.[24]

Several neuropsychiatric symptoms and disorders, including dizziness, confusion, delirium, and psychosis have also been reported. For instance, when an online network of researchers in the UK composed of neuroscientists, neurologists, psychiatrists, and intensive care specialists examined over 100 patient cases identified in April 2020, altered mental states were noted as the second most common presentation.[23] The majority (59%) of these patients displayed altered mental states that met criteria for diagnosis as determined by a psychiatrist or neuropsychiatrist. Importantly, nearly all of these cases (92%) were new diagnoses. Among the individuals showing altered mental states, the most common diagnoses were psychosis (43%), dementia-like syndromes (26%), and affective disorders (17%). While some symptoms were most common in older patients, nearly half (49%) of the patients with altered mental states were younger than 60 years of age. Experiences of delirium and mental disturbance may be compounded by the treatment of COVID-19 in hospitals, which often imposes social isolation, little or no physical contact with loved ones, and restricted movement from one's treatment space.[5,9,14]

Seizure and strokes have also been reported among COVID-19 patients. For instance, among 43 confirmed or likely cases of COVID-19 in the UK in March 2020, Paterson et al (2020) found that 8 (19%) had ischemic strokes. Similarly, of 125 patients presenting with a cerebrovascular event in the UK in April 2020, Varatharaj and colleagues (2020) found that 57 (74%) had ischemic strokes, 9 (12%) showed hemorrhaging in the brain, and 1 (1%) showed vasculitis (inflammation) in the brain and spinal cord. Early case studies also report seizures.[13,25]

NEUROLOGICAL CONSEQUENCES AFTER ACUTE COVID-19

Even after recovering from COVID-19, an individual may suffer from ongoing neurological challenges, which could be linked with what many call "long COVID."[8] For instance, a recent examination of cognitive test scores from 84,285 individuals in the UK, including those with confirmed or suspected COVID-19 infection as of May 2020, found that people who had recovered and were no longer symptomatic displayed significant cognitive

deficits as compared to controls.[7] This effect does not appear to be the result of individual characteristics that may distinguish cases and controls; differences remain when controlling for variables, such as age, gender, education, income, ethnicity, and previous medical disorders. Cognitive impairments when performing tests of semantic problem solving, spatial working memory, selective attention, and emotional processing were most severe for those who had been hospitalized, and larger for those who had been on a ventilator than for those who had not (ventilated: -0.57 SDs $n = 60$ vs. not: -0.45SDs $n = 147$).[7] However, impairments were also detectable among individuals with confirmed cases without breathing impairment, suggesting that deficits may "scale with symptom severity" and impact a sizable portion of people who become infected. These findings are striking but require cautious interpretation because individuals were not followed over time with pre- and post-diagnosis assessments.

There is some concern that COVID-19 may lead to long-term neurological or other challenges for survivors even after acute infection resolves,[4,6,22] especially among those who experienced numerous or severe symptoms during the disease.[3] For instance, data from January 2020 from 62,354 people in the UK reveals that COVID-19 survivors with no history of neuropsychiatric disorder were approximately twice as likely to display a disorder, including insomnia and dementia, at three-month follow-up than people who experienced other respiratory tract infections like influenza, or other health concerns.[21] Moreover, encephalitis, hypoxia, and strokes are well known causes of long-term and, in some cases, permanent neurocognitive damage. Consistent with these risks, autopsies examining the brains of individuals who died due to COVID-19 in April 2020 showed signs of inflammatory changes, encephalitis, vascular changes, microhaemorrhages, hypoxia, and ischaemic brain lesions.[20]

CONCLUSION

In summary, evidence of the neurological consequences of COVID-19 is heterogeneous, tentative, and rapidly evolving. To date, the evidence suggests that COVID-19 very likely affects the nervous system and manifests in neurological symptoms, some of which may be long lasting. The mechanisms of the infection are still unclear, but studies suggest that infection of the nervous system, vascular pathologies, systemic inflammatory response, immune-mediated mechanisms, and/or treatment related factors may be responsible.[11,15,18] This knowledge should inform clinical guidelines, assessment, and public health planning while more systematic and longitudinal research provides further insights.

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