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Review

COVID-19: NEUROLOGICAL SEQUELAE

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COVID-19, the human primarily respiratory disease caused by the coronavirus SARS-CoV-2, commonly involves the nervous system, the effects of which may persist for many months. Post-acute sequelae of COVID-19 include relapsing and remitting neurological and neuropsychiatric symptoms that can affect children and adults, including those who had mild acute illness. Since longer-term adverse effects on the central and peripheral nervous system of COVID-19 cannot be excluded, patient and societal health trends should be monitored going forward. Urgent present needs include not only global immunization against SARS-CoV-2 but also the reestablishment of lapsed mass vaccination programs to prevent resurgence of other viral diseases (e.g., measles, polio) that can impact the nervous system.

Key words: *SARS-CoV-2, PASC: post-acute sequelae of SARS-CoV-2 (Long Covid), vaccines.*

COVID-19 Origins. The COVID-19 pandemic appears to have begun in China at the end of 2019 from the prior transfer of an enveloped single-strand RNA virus from a wild animal (probably the horseshoe bat) to humans, possibly via an intermediate host, with subsequent efficient human-to-human transmission that was first recognized in Hubei province in central China [1–7]. Given the country's recent experience with human and animal coronavirus diseases, including Severe Acute Respiratory Syndrome (SARS) and Swine Acute Diarrhea Syndrome, Chinese scientists predicted in March 2019 that coronaviruses acquired from bats would cause a future SARS-like outbreak of human disease, most probably in China [8]. In 2020, SARS-CoV-2 and mutants thereof had spread around the world and, by May 1, 2021, the World Health Organization reported >150 million confirmed cases of COVID-19, with an average fatality rate of 2.1 %.

Acute COVID-19. SARS-CoV-2 targets, enters and replicates in cells with angiotensin converting enzyme two (ACE2) receptors throughout the human body, including the nervous system [9–14]. Persons with relative ACE2 deficiency, including the elderly and those with preexisting non-communicable health disorders (hypertension, diabetes, cardiovascular disease or cancer), have a higher risk for severe COVID-19 [15–17]. The immune system targets the foreign SARS-CoV-2 spike protein resulting in local inflammation

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and generation of cytokines and chemokines. Infection of the vascular endothelium may disrupt the blood-brain barrier [18], promote a hypercoagulable state, and increase the risk for arterial and venous thrombosis. While pulmonary and cardiovascular dysfunction usually dominate the acute phase of the illness, many patients experience neurological symptoms (headache, dizziness, fatigue, reduction/loss of smell and taste, myalgia), signs (altered mental status), and unusual/rare disorders (seizures, meningitis, encephalitis, encephalopathy, transverse myelitis, and Guillain-Barre syndrome, among others) [19–28]. COVID-19 has not increased the incidence of epilepsy but has presented patient management and therapeutic challenges [29, 30]. The proportion of patients with COVID-19 reported to have acute new onset neurological disease or symptoms varies significantly depending on the study population, availability of assessment and many other factors; the proportion of these patients in the hospitalized population is also heterogeneous, but in most studies is reported to be 30–60 % [31].

SARS-CoV-2 Distribution. While SARS-CoV-2 is readily detected by reverse transcriptase quantitative polymerase chain reaction in bronchial fluid, sputum, nasal and pharyngeal swabs, detection of virus in serum has varied from 0–40 % [32]. The virus or corresponding antibodies have been only occasionally detected in cerebrospinal fluid and brain tissue [27, 32–35]. Unproven is whether the virus can enter the brain via axonal transfer from nerve terminals in the olfactory and pulmonary epithelium or via the glossopharyngeal, trigeminal and vagus nerves [10, 26]. Neuropathological studies conducted post-mortem have demonstrated multifocal microvascular injury with fibrinogen leakage, microthrombi and spontaneous hemorrhage, perivascular activated microglia, microglial nodules, macrophage infiltrates, and astrogliosis, with neuronophagia in the olfactory bulb, substantia nigra, dorsal vagal motor nucleus, and the medullary respiratory center [33, 36]. Thirty percent of cases in one study showed acute-hypoxic-ischemic changes [33]. Viral protein has been detected in the medulla oblongata and proximal regions of cranial nerves IX and X in association with marked brainstem inflammation attributed to localized immunological responses (cytokine storm) and/or to SARS-CoV-2 infection [37]. Nigrostriatal dopamine dysfunction was reported in three patients who developed parkinsonism 2–5 weeks after severe SARS-CoV-2 respiratory infection [38].

Post-Acute SARS-CoV-2 («Long-COVID»). Virus-associated CNS effects, whether anoxic/ischemic, hemorrhagic or encephalitic in origin, together with damage to other organs (notably, lungs, kidneys and heart) in those with severe COVID-19, compromise health post-hospitalization, especially for those with comorbidities, and result in increased use of medications and excess deaths after 6 months [16, 21, 39–44]. In addition, a significant percentage of adults and children, including those who had mild acute COVID-19, develop post-acute sequelae of SARS-CoV-2 (PASC) [45, 46] that may persist for at least 6 months following the original illness [47, 48] (Figure), with features similar to the pos-SARS syndrome and that overlap with Chronic Fatigue Syndrome and Functional Neurological Disorder [24, 28, 49].

PASC, also known as Long-COVID [50], which is more common in females than males, includes the following manifestations: neurological/neuropsychiatric symptoms (fogginess, headache, dizziness, loss of attention, confusion, mood disorders, sleep-wake disturbances, hyposmia/anosmia and dysgeusia/ageusia), as well as disorders of the gastrointestinal system (abdominal pain, diarrhea) and cardiorespiratory and musculoskeletal systems (fatigue, exercise intolerance, myalgias, dyspnea, cough, arthralgias) [46, 48]. Long-lasting symptoms consistent with autonomic function (breathlessness, chest pain, palpitations and orthostatic intolerance) are also reported [50]. In Moscow, a telephone

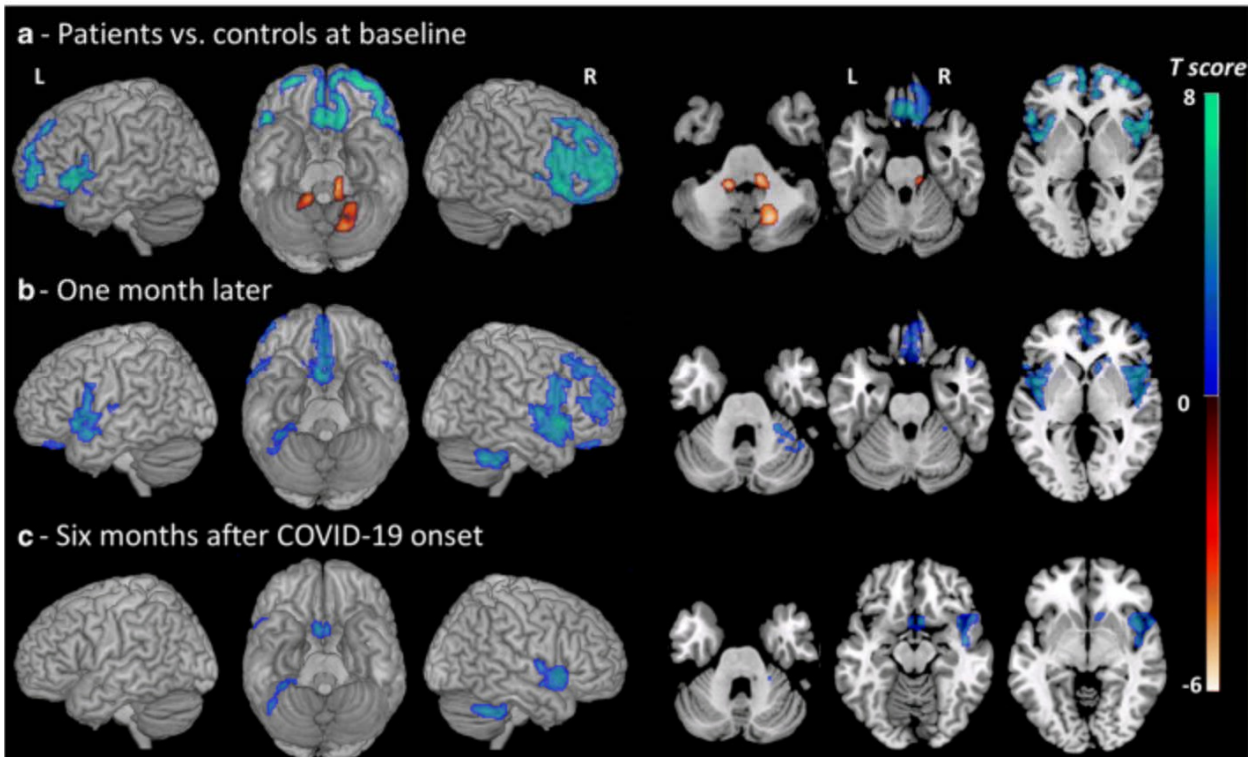

Figure. Brain metabolism changes in COVID-19

N o t e : Brain metabolism changes in COVID-19. Once in the acute phase, 1 month later and 6 months after COVID-19 onset, brain metabolism of seven patients ($n = 7$) with variable clinical presentations of COVID-19-related encephalopathy were examined with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). PET images were analyzed with voxel-wise and regions-of-interest approaches in comparison with 32 healthy controls. Hot and cool color scales show regions with hypermetabolism and hypometabolism in patients vs. controls, respectively. Statistical Parametric Maps (https: //www.fil.ion.ucl.ac.uk/spm/) are projected onto a surface rendering and onto axial views of the customized magnetic resonance imaging template. The axial slices are shown using neurological conventions (right is right). R, right; L, left. At baseline, hypometabolism was found in the bilateral prefrontal cortex with right predominance, insula, anterior cingulate and caudate ($p < 0.05$ corrected). Analysis showed a mild hypermetabolism in the cerebellar vermis, dentate nucleus and pons ($p < 0.05$). One month later, hypometabolism was limited to the mediofrontal, right dorsolateral areas, olfactory/rectus gyrus, bilateral insula, right caudate nucleus and cerebellum ($p < 0.001$). Six months after COVID-19 onset, decreased metabolism was observed in the same regions but they were less extended ($p < 0.001$). At this timepoint, the majority of patients had improved clinically but cognitive and emotional disorders of varying severity remained with attention/executive disabilities and anxio-depressive symptoms. Reproduced from Figure 1, legend, and extracted text of Kas A, Soret M, Pyatigoskaya N, Habert MO, Hesters A, Le Guennec L, Paccoud O, Bombois S, Delorme C; on the behalf of CoCo-Neurosciences study group and COVID SMIT PSL study group. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. Eur J Nucl Med Mol Imaging 2021 Jan 15: 1–15. doi: 10.1007/s00259-020-05178-y. [Authors own copyright under exclusive license to Springer-Verlag GmbH, DE part of Springer Nature 2021, with article available via the PubMed Central Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.]

interview study of 2640 COVID-19 male and female patients 6–8 months after their hospital discharge recorded significant fatigue (~21 %), shortness of breath (~14 %) and forgetfulness (~9 %), mood disorders and behavioral changes [45]. In the USA, a large case-control study of non-hospitalized veterans 1–6 months after illness onset found an excess of nervous system, neurocognitive and mental health disorders, and metabolic, gastrointestinal and cardiovascular disorders, including anemia, malaise, fatigue, and muscu-

loskeletal pain, increased use of opioid and non-opioid medication and excess deaths (8/1000) among COVID-19 survivors [39].

Longerterm Concerns. COVID-19 patients might have a higher risk for delayed/long-term neurological and neuropsychiatric sequelae [51, 52]. Persistent hyposmia following SARS-CoV-2 infection is of note because this symptom is an early but non-specific marker of Alzheimer disease, a prominent genetic risk factor (ApoE4) for which is associated with severe COVID-19 [23, 54, 55]. Unknown is whether reservoirs of SARS-CoV-2 remain in immunologically privileged sites (eye, testes, brain), comparable to the persistence of human coronavirus OC43 in mouse brain [27]. ACE2 receptors are present in the human eye [11] where other viruses (Ebola, Marburg or Rubella) can reside after clearance from the systemic circulation [56, 57, 58]. Measles Virus can develop hypermutated forms in vivo that establish latent neuronal infection which, in the event of subsequent immunosuppression, can reactivate and precipitate the fatal neurological illness Subacute Sclerosing Panencephalitis (SSPE) [59, 30]. Persistent or latent brain infection with SARS-CoV-2 is unlikely but has not been ruled out. However, COVID-19 has disrupted global vaccination campaigns, including those for measles, mumps and rubella (MMR) which, given the progressive loss of MMR immunity over time, may result in a resurgence of measles and even higher rates of SSPE in at-risk countries, such as those in southern Asia [60, 61, 62].

In conclusion, SARS-CoV-2 produces a systemic transmissible infection that often impacts the nervous system in the short- and longer-term [63]. In addition to cardiopulmonary and hematogenous disorders that secondarily precipitate brain hypoxic disease, coronaviruses can invade the nervous system and trigger neurological disorders arising from the host's immune response and/or viral propagation in the nervous system [63, 64]. There is an urgent need for global SARS-CoV-2 immunization not only to prevent COVID-19 but also to restore mass vaccination campaigns for common infectious diseases that existed prior to the present pandemic.

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