CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Cognitive Deficits in Long Covid-19

Varun Venkataramani, M.D., Ph.D., and Frank Winkler, M.D., Ph.D.

Some patients who have recovered from an infection have reported transient or even lasting cognitive dysfunction. This includes patients who have been infected with SARS-CoV-2, many of whom, including those with mild disease, have reported deficits in attention, executive functioning, language, processing speed, and memory — symptoms collectively referred to as "brain fog." Together with increased incidence of anxiety, depression, sleep disorder, and fatigue, this syndrome of cognitive impairment contributes substantially to the morbidity of post–Covid-19 conditions (also called "long Covid").

Nevertheless, Covid-related brain fog is difficult to diagnose and to separate from other reasons for the symptoms in an individual patient, because neurocognitive longitudinal data for patients are rarely available. (On a population level, however, cognitive decline after Covid has been documented.[1]) Physicians are generally reluctant to accept a condition as an organic disease without a pathobiologic concept or the ability to measure the disease in a given patient, as is the case with post-Covid brain fog. Results of a study recently reported by Fernández-Castañeda and colleagues may represent a pivot in our understanding of this sequela.[2]

Using a mouse model, the investigators explored how mild respiratory infections of SARS-CoV-2 could lead to neuroinflammation and subsequent brain damage through multilineage neural cell dysregulation (Fig. 1). The investigators modeled mild respiratory Covid in a mouse expressing the viral-entry receptor for SARS-CoV-2 (angiotensin-converting enzyme 2 in humans) in the trachea and lung by delivering SARS-CoV-2 intranasally. They detected no SARS-CoV-2 in the brain but found signs of neuroinflammation in elevated levels of chemokines in cerebrospinal fluid and serum, each with a distinct time course. These changes led to activation of microglia in subcortical and hippocampal white-matter regions (but not in gray matter), with distinct effects on specific neural cell populations. Of note, these findings were supported by similar results in a small group of patients who were found to have SARS-CoV-2 infection and no severe lung damage at the time of death.

Microglia are resident macrophage cells in the central nervous system. Although they contribute to the homeostasis of the central nervous system and refinement of neuronal networks by removing dendritic spines and synapses during the development of neurons, microglia can transition to an activated, neurotoxic state, as seen in this mouse model. In the subcortical white matter, microglial activation was associated with loss of both oligodendrocyte precursors and mature oligodendrocytes; consistent with this loss, there was also loss of myelin and myelinated axons for at least 7 weeks after the infection began. Myelin insulates axons and is critical to the speed of electrical conduction along neurons and to axonal metabolism. The loss of myelinated axons impairs the structure and function of neuronal networks.

In the hippocampus, the activation of microglia was associated with inhibited neurogenesis, which could explain impaired memory formation in patients. The activation of microglia appeared to be mediated by persistently elevated levels of a molecule called C-C motif chemokine 11 (CCL11). CCL11 has been associated with aging and with inhibition of neurogenesis.[3] Systemic intraperitoneal injection of CCL11 into mice resulted in the activation of hippocampal microglia but not microglia in the subcortical white matter. Consistent with these findings, persons with long Covid and cognitive deficits

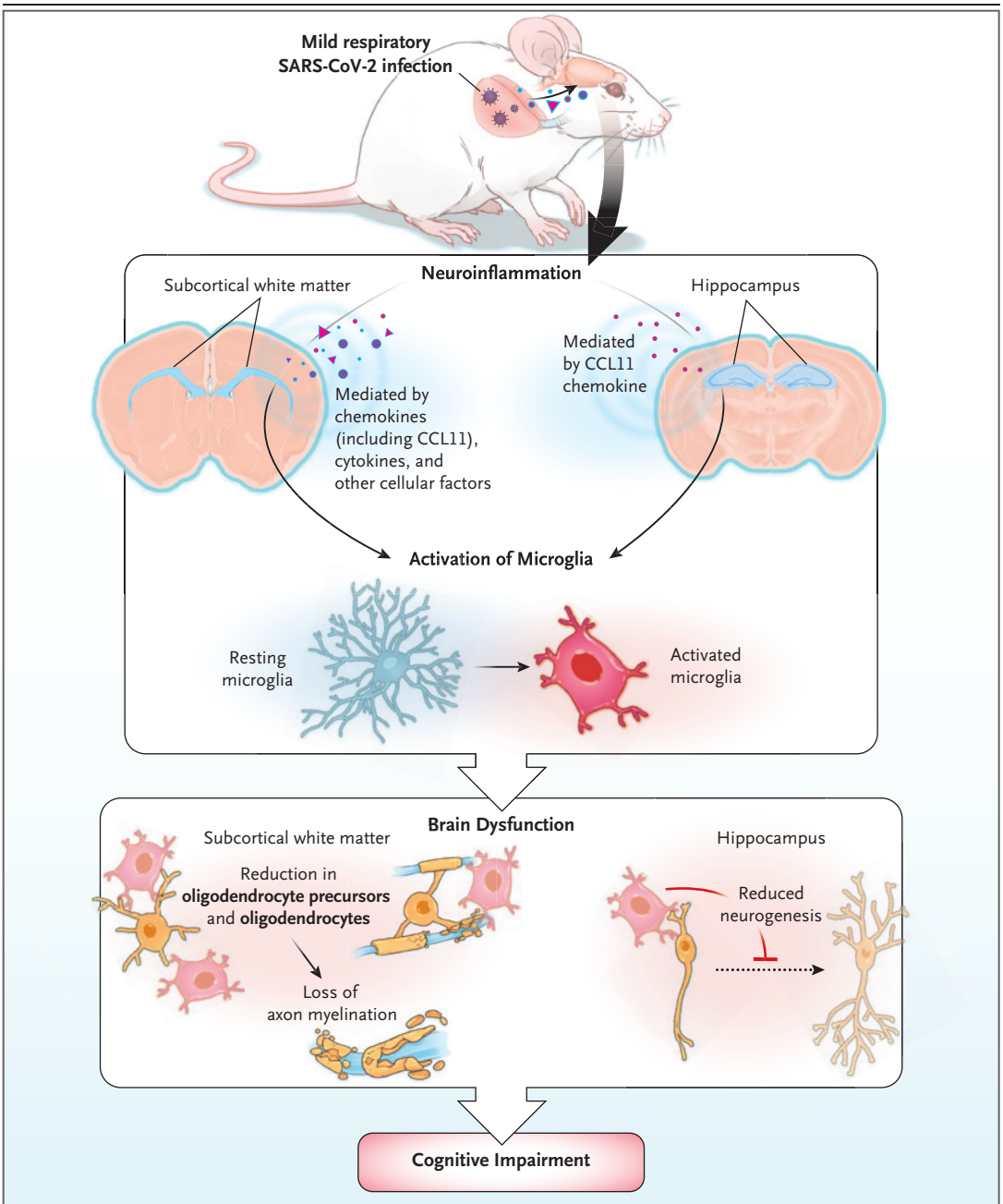

Figure 1. Effect of Mild Respiratory SARS-CoV-2 Infection on Neural Cells.

In a recent study, Fernández-Castañeda et al.[2] investigated the effects of mild respiratory SARS-CoV-2 infection in a mouse model. They detected changes in neuroinflammatory cytokines and chemokines, including the protein C-C motif chemokine 11 (CCL11), in the cerebrospinal fluid and serum over a period of 7 weeks after initiation of infection. They also observed changes specific to the brain regions of the subcortical white matter, with microglia activation and subsequent loss of oligodendrocytes, oligodendrocyte-precursor cells, and myelin. Intraperitoneal delivery of CCL11 to an unaffected mouse induced activation of microglia and inhibited neurogenesis. Taken together, these mechanisms could explain brain dysfunction and cognitive impairment.

had higher levels of serum CCL11 than those with long Covid who lacked cognitive symptoms. The patients, like the mice, had mild disease, and they were infected before the availability of vaccines, but their numbers were small (48 with cognitive deficits and 15 without them).

The effect of CCL11 on microglial activation in the hippocampus and inhibition of neurogenesis warrants further exploration of the effects of chemokines and cytokines specific to brain circuits and potentially offers a framework to study, prevent, and treat the neurologic and psychiatric symptoms of long Covid. The findings of Fernández-Castañeda et al. also have pathobiologic parallels to the cognitive impairment syndromes that have occurred after cancer therapy[4] and after H1N1 influenza infection. (The investigators also found a temporal correlation between elevated levels of chemokines and cytokines and impaired hippocampal neurogenesis after H1N1 infection in a mouse model.)

Could these findings lead to a cure for Covid-related brain fog? Several drugs that target activated microglia have been tested in preclinical models of mechanistically similar syndromes of cognitive impairment. Pexidartinib, an inhibitor of the CSF1 receptor, has been approved by the Food and Drug Administration for the treatment of symptomatic tenosynovial giant-cell tumors and can deplete microglia. Certain nonsteroidal antiinflammatory agents and tetracyclines can inhibit microglia. Findings from the study by Fernández-Castañeda and colleagues support the testing of microglial modulators to treat Covid-related brain fog. Study of the targeting of upstream regulators of microglial activation like CCL11 could also be beneficial.

The study also implicates CCL11 as a candidate biomarker. If this finding is validated through future study, levels of CCL11 in the plasma or cerebrospinal fluid could potentially identify patients with Covid-related cognitive impairment. Assays of CCL11 could also be used to study the effect of vaccinations against Covid on brain fog–related changes. However, because only small patient cohorts were studied and factors such as a patient's sex and history of autoimmune disease may influence serum levels of CCL11, large cohort clinical studies are needed to exclude confounder variables and further substantiate CCL11 as a biomarker. Specificity may increase when other cytokine or chemokine profiles are included or with a narrower focus on CCL11 levels in the cerebrospinal fluid, since there is a substantial overlap of CCL11 serum levels in persons with brain fog and those without.

The finding of axonal demyelination (or impaired myelination) in sections of mouse brain could inspire the development of new magnetic resonance imaging biomarkers for humans.[1] It should be noted, however, that Fernández-Castañeda et al. used the earliest strain of SARS-CoV-2 (known as the original Wuhan-Hu-1 isolate or USA-WA1/2020); the relevance of their findings to brain fog associated with infection by other SARS-CoV-2 variants seems likely but uncertain. Moreover, as the authors themselves noted, the contribution of other cell types, such as astrocytes, to Covid-related brain fog may be substantive. Finally, there is the usual caveat that mice are not humans, so these findings warrant robust tests of replication in studies involving a larger number of patients. Although the findings of brain dysfunction and patterns of damage during and after Covid are worrisome, especially given the similarities with changes in human neurodegenerative diseases,[5] translational studies such as the one reported by Fernández-Castañeda may point to paths toward accurate diagnoses and treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany.

1. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 2022;604:697-707.
2. Fernández-Castañeda A, Lu P, Geraghty AC, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell 2022;185(14):2452-2468.e16.
3. Villeda SA, Luo J, Mosher KI, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 2011;477:90-4.
4. Gibson EM, Nagaraja S, Ocampo A, et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. Cell 2019;176(1):43-55.e13.
5. Yang AC, Kern F, Losada PM, et al. Dysregulation of brain and choroid plexus cell types in severe COVID-19. Nature 2021;595:565-71.

DOI: 10.1056/NEJMcibr2210069