The use of nitrogen-rich fertilizers and their runoff into waterways are major contributors to the growing imbalance of nitrogen and phosphorus.

communities (*8*). The impact of the imbalance will continue to increase as the imbalance continues to tip in the same direction.

This increasing N/P imbalance can have severe consequences not only for natural ecosystems but also for human societies because crop production and food security will be affected. The resource gap in remedying this imbalance at the regional level may also broaden the economic gap between rich and poor countries (*9*). N-containing fertilizers have an unlimited source—the atmosphere—from which N can be extracted through the Haber-Bösh reaction. This innovation has allowed a continuous increase in the production and use of these N fertilizers since the 1950s (*10*). By comparison, P sources have largely been limited to mines and are concentrated in very few countries, such as Morocco (*9*), so P might eventually become economically inaccessible to low-income and food-deficient countries as these sources become depleted. In the future, P-producing nations are likely to manage their reserves to maximize profit for both their domestic mining and farming industries, making P-based fertilizers increasingly unaffordable for farmers in the poorest countries (*9*) and worsening the N/P imbalance in regions where the problem is the most prominent.

Imbalanced soil N/P ratios can also affect the chemical composition of crops, which can have implications on public health. For example, in some regions P accumulates in soils and water bodies, and the N/P ratio decreases, as a result of an excessive use of inorganic and organic P fertilizers (*3*). Food produced in these environments may lead to an overconsumption of P in the local population, which can have negative implications for their health (*11*). The implications of this global imbalance between N and P could also have impacts on several other human infectious and noninfectious illnesses that are strongly associated with diet, such as coeliac disease (*12*).

Besides the imbalance observed in the N/P ratio, human activities also generate imbalances among other elements. For example, changes in the ratio of carbon (C) and N relative to iron, zinc, calcium, and potassium, among others, have been observed in plant tissues (*12*). The increasing atmospheric concentrations of CO_2 are likely a driver of the increase of C in plants, which in turn have developed more compounds that reduce the concentrations of these other elements (*12*). This indirectly leads to the displacement of the elemental composition (elementome) (*13*) of organisms, communities, and entire ecosystems owing to imbalances of the anthropogenic biospheric inputs of C and N relative to P and other elements in recent decades and is likely to exacerbate in the coming decades.

The time has come for national and international environmental agencies and policymakers to recognize the risks of unbalanced N/P ratios and other parallel imbalances in elemental stoichiometry to the biosphere and humanity. The international environmental agencies and policy-makers should address the problem through a coordinated international policy. Observations, experimentation, theory, and modeling at different temporal and spatial scales are warranted to evaluate, predict, and provide possible solutions to these anthropogenic nutritional imbalances and their effects on nature and humans. Among these possible solutions, increasing the efficiency of use and cycling of N and P—for example, through precision agriculture to avoid misuse of fertilizers, methods to increase plant accessibility to P sources, use of innovative management techniques and biotechnologies to improve nutrient-use efficiency, stimuli and subsidies for recycling P through legislative regulations and instruments at the national or regional administrative level, or reduction of livestock production—has been suggested as the most effective approach to prevent imbalanced N/P ratios for food production and reduce environmental problems that involve N and P. This research will determine whether these nutritional imbalances should be added to the planetary boundaries instead of only considering N and P separately (*14*). ■

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VIEWPOINT: COVID-19

Nervous system consequences of COVID-19

Neurological symptoms highlight the need to understand pathophysiologic mechanisms

By **Serena Spudich**[1] *and* **Avindra Nath**[2]

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered a respiratory pathogen, myriad neurologic complications—including confusion, stroke, and neuromuscular disorders—manifest during acute COVID-19. Furthermore, maladies such as impaired concentration, headache, sensory disturbances, depression, and even psychosis may persist for months after infection, as part of a constellation of symptoms now called Long Covid. Even young people with mild initial disease can develop acute COVID-19 and Long Covid neuropsychiatric syndromes. The pathophysiological mechanisms are not well understood, although evidence primarily implicates immune dysfunction, including nonspecific neuroinflammation and antineural autoimmune dysregulation. It is uncertain whether unforeseen neurological consequences may develop years after initial infection. With millions of individuals affected, nervous system complications pose public health challenges for rehabilitation and recovery and for disruptions in the workforce due to loss of functional capacity. There is an urgent need to understand the pathophysiology of these disorders and develop disease-modifying therapies.

Initial reports of neurologic syndromes accompanying COVID-19 described changes in level of consciousness or cognitive dysfunction, weakness, and headache in hospitalized patients that might be attributable to any severe acute illness with respiratory and metabolic disturbances. Subsequently, reports of strokes and acute inflammation

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or demyelination of the central or peripheral nervous system highlighted specific cerebrovascular and neural tissue involvement. As the number of cases increased globally, it was recognized that SARS-CoV-2 not only induces respiratory symptoms but also can affect multiple organ systems, including the kidneys, gastrointestinal tract, heart, and brain.

Clinical neurological and psychiatric syndromes in patients with acute COVID-19 have been delineated by surveillance studies of hospitalized patients. A UK-wide study of hospitalized patients identified the most common neurologic conditions as anosmia (loss of smell), stroke, delirium, brain inflammation, encephalopathy, primary psychiatric syndromes, and peripheral nerve syndromes (*1*). Varied timing of onset suggests that these conditions have diverse pathophysiological mechanisms. For example, cerebrovascular complications co-occur with or even predate the onset of respiratory symptoms, whereas central inflammatory and peripheral nerve conditions manifest on average 2 weeks later, suggesting that they may result from peri- or postinfectious processes (*2*).

Despite early speculation that SARS-CoV-2 may enter the central nervous system (CNS) via migration through the nasal cavity and the olfactory pathway or trafficking across the blood-brain barrier, analysis of cerebrospinal fluid (CSF) from living patients with neuropsychiatric manifestations has almost uniformly failed to detect viral RNA by reverse transcription polymerase chain reaction. Instead, the preponderance of evidence from CSF and brain tissue suggests that immune activation and inflammation within the CNS is the primary driver of neurologic disease in acute COVID-19. Indeed, histopathological studies of brain tissue from patients who died with acute COVID-19 reveal only limited detection of SARS-CoV-2 nucleic acid or viral protein in the brain (*3, 4*), consistent with findings in CSF from live patients. Direct examination of autopsy brain tissue has caveats—those who died with acute COVID-19 had severe disease that may not be representative of the majority of those infected with SARS-CoV-2. Many had systemic or metabolic derangements prior to death that may contribute to pathology in a nonspecific way. However, when infrequently detected, infected cells in human brain lack surrounding clusters of inflammatory cells, suggesting that SARS-CoV-2 presence in the CNS does not incite classic viral encephalitis.

Examination of CSF samples from living patients reveals neuroinflammation and aberrant neuroimmune responses during acute COVID-19. CSF shows up-regulation in the expression of interferon-regulated genes in dendritic cells, along with activated T cells and natural killer (NK) cells. This is accompanied with an increase in interleukin-1 (IL-1) and IL-12, which is not seen in blood plasma (*5*). Additionally, CSF-specific clonal expansion of T cells and antibodies that recognize epitopes of SARS-CoV-2 spike protein that cross-react with neural antigens suggest compartmentalization of the immune response (*5, 6*), although the possibility of a persistent infection with restricted viral replication cannot be entirely excluded. During this acute phase, other markers of monocyte activation and neuronal injury can also be detected in CSF (*7*). In the following subacute phase, patients with severe manifestations show diminished interferon responses and markers of T cell exhaustion in CSF (*8*).

"Many people who experience neurologic symptoms that linger after acute COVID-19 are less than 50 years old and were healthy and active prior to infection."

Autopsy studies of patients with acute COVID-19 show infiltration of macrophages, $CD8^+$ T lymphocytes in perivascular regions, and widespread microglial activation throughout the brain (*3*). Single-cell analysis of brain tissue has also confirmed $CD8^+$ T lymphocyte infiltration and microglial activation without evidence of SARS-CoV-2 RNA detection in cells of the brain parenchyma (*9*). The robust, generalized, and SARS-CoV-2–specific immune responses observed in the CNS are puzzling in the absence of readily detectable virus and may suggest transient infection of the brain very early in infection or low concentrations of viral antigen in the CNS. Systemic activation of immune cells may additionally lead to up-regulated expression of cell surface markers that facilitate amplified trafficking into the nervous system, even in the absence of targeted CNS antigens (see the figure).

Does widespread vascular dysfunction contribute to nervous system complications of COVID-19? Acute COVID-19 is associated with heightened risk of stroke compared with influenza illness of similar severity, even after correcting for stroke risk factors (*10*). Overt cerebrovascular events during acute COVID-19 often occur in those with vulnerabilities to vascular disease (such as advanced age and cardiac disease). Increases in blood markers of vascular inflammation as well as thrombosis and infarction in other tissues can also be found in patients with COVID-19 and stroke, suggesting that endothelial inflammation and coagulopathy contribute to these events (*11*). Indeed, system-wide vascular dysfunction can characterize severe acute COVID-19 and has the potential to contribute to manifestations of organ system failure and systemic inflammation in those most severely ill (*12*). It is plausible that subtle forms of generalized vascular dysfunction, including thrombotic microangiopathy (microscopic blood clots) in the brain, may lead to neurological symptoms even in the absence of clinically apparent stroke. Additionally, high-field magnetic resonance examination of brain tissue demonstrates microvascular damage in structures plausibly related to neurologic manifestations of COVID-19, consistent with endothelial activation and widespread vascular injury observed in other organs (*4*).

Since early in the COVID-19 pandemic, patients have described lingering syndromes following acute infection, now called Long Covid. These syndromes often include predominant neurologic and psychiatric symptoms, such as difficulty with memory, concentration, and ability to accomplish everyday tasks, frequent headaches, alterations in skin sensation, autonomic dysfunction, intractable fatigue, and in severe cases, delusions and paranoia. Many people who experience neurologic symptoms that linger after acute COVID-19 are less than 50 years old and were healthy and active prior to infection. Notably, the majority were never hospitalized during their acute COVID-19 illness, reflecting mild initial disease. Many of the symptoms experienced by individuals with Long Covid are similar to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is also considered to be a postinfectious syndrome caused by a variety of infectious agents. Because the pathophysiology of ME/CFS is poorly understood and there are no effective disease-modifying therapies available, it is likely that the study of Long Covid may benefit ME/CFS patients as well. There is also overlap in symptoms of post–Lyme disease, suggesting that there may be common host susceptibility factors that underlie these illnesses.

The heterogeneity of symptoms affecting individuals with Long Covid and the difficulties in ascertaining which symptoms may be a consequence of SARS-CoV-2 in-

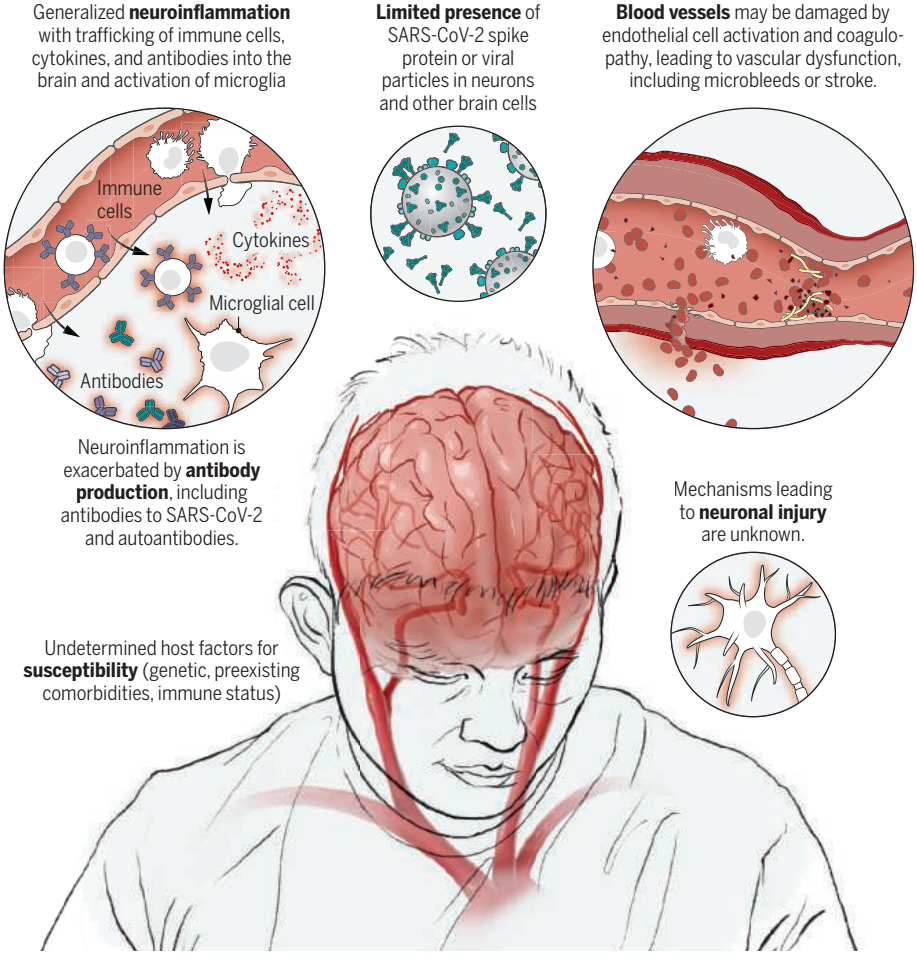
fection versus aggravation of preexisting or coincidental conditions pose enormous challenges for mechanistic understanding and approaches to treatment. Few studies have systematically categorized or examined the natural history of Long Covid symptoms, let alone studied their biology. Of 3762 respondents in an online study of people with persistent symptoms after documented or suspected COVID-19, many had ongoing symptoms up to 7 months after initial infection, including prominent neuropsychiatric syndromes (*13*). Serial imaging routinely captured in the UK Biobank cohort has revealed focal areas of brain atrophy in individuals after documented COVID-19 compared with a parallel group without COVID-19, suggesting a potential biomarker for brain effects of SARS-CoV-2 (*14*). Studies of positron emission tomography (PET) imaging also show decreased metabolic activity in the brain in people with Long Covid (*15*). However, the pathophysiology leading to these symptoms and cerebral changes is unknown. Potential etiologies are mainly extrapolated from current understanding of nervous system pathogenesis during acute COVID-19. These include residual immune activation or persistent autoimmune disturbance, ongoing endothelial activation or vascular dysfunction, or residua of injury accrued during acute disease. Systematic neurologic studies of carefully phenotyped individuals with neurological Long Covid symptoms are essential. These patients often also experience stigma, employment difficulties, and mental health challenges. Thus, diagnostic certainty and therapeutic interventions are needed to address this major public health concern.

The full extent of the long-term neurological complications of COVID-19 has not been realized. Observations of neuroinflammation and neuronal injury in acute COVID-19 have raised the possibility that infection may accelerate or trigger future development of neurodegenerative diseases such as Alzheimer's or Parkinson's diseases. No information is yet available regarding neurodevelopmental trajectories in children, who usually experience mild COVID-19 and manifest few neurologic or psychiatric symptoms during or after acute illness. Those who experience the rare multisystem-inflammatory syndrome in children (MIS-C) may be at particular risk for neurological sequelae owing to widespread endothelial activation, often involving the brain.

What are the host factors that account for the wide variability in clinical manifestations such that some patients develop acute neurologic illness, and others develop persistent postinfectious complications? It will be critical to characterize the pattern(s) of immune dysregulation in Long Covid patients. Is it possible that persistent immune dysregulation underlies ongoing symptoms? If so, this may be driven by host antigens with autoimmune responses, or a persistent viral infection with restricted viral replication in tissue reservoirs. Whether antiviral or immune-targeted interventions early in the disease course or prophylactic vaccination against COVID-19 will alter the trajectory of neurologic complications of COVID-19 is also unknown. Investigations that include longitudinal studies with neurological and psychiatric assessments and rigorous host-pathogen studies of systemic and nervous system interactions have the potential to answer these questions. Ultimately, interventional trials based on these discoveries are needed to determine approaches to curtail or reverse nervous system effects of COVID-19 that are experienced by huge numbers of people globally. ■

Putative neuropathogenic effects of SARS-CoV-2

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to neuropsychiatric effects during acute COVID-19, including confusion, stroke, and neuromuscular disorders. These may arise from neuroinflammation, coagulopathy, neuronal injury, and possibly viral infection in the central nervous system. Causes of Long Covid symptoms affecting the nervous system may result from the emergence and persistence of these mechanisms.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*

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