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Neurological Aspects of COVID-19: Acute and Long-Term Manifestations in Adults and Children

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Abstract

Coronavirus disease 2019 (COVID-19) is now recognized as a multisystem illness with prominent neurological involvement. Both acute infection and post-acute sequelae (“long COVID”) are frequently accompanied by neurologic and neuropsychiatric symptoms in adults and children. This narrative review summarizes current evidence on the neurological aspects of COVID-19, including mechanisms, clinical manifestations, imaging findings and treatment. SARS-CoV-2 may access the nervous system via hematogenous routes and possibly cranial nerves, but most injury appears to result from systemic inflammation, endothelial dysfunction, coagulopathy and post-infectious autoimmunity rather than widespread direct neuronal infection. In adults, acute presentations range from headache, anosmia and encephalopathy to ischemic and hemorrhagic stroke, inflammatory CNS syndromes, seizures and Guillain–Barré syndrome. Children show a similar but age-dependent spectrum, with neurologic complications particularly prominent in multisystem inflammatory syndrome in children (MIS-C). Long COVID is characterized by persistent cognitive impairment, fatigue, sleep disturbance, dysautonomia, chronic headache, neuropathic symptoms and mood disorders, with generally milder but comparable patterns in adolescents. Acute neuroimaging often demonstrates infarcts, hemorrhage, microbleeds, leukoencephalopathy, PRES or transient splenial lesions, whereas conventional imaging in long COVID is usually normal despite subtle changes on advanced MRI and PET. Early recognition, guideline-based management of acute events, and multidisciplinary rehabilitation for long-term sequelae are crucial while ongoing studies clarify mechanisms and optimal therapies.

Keywords: COVID-19; SARS-CoV-2; neurological manifestations; encephalopathy; stroke; long COVID.

Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is now recognized as a multisystem disorder. In addition to respiratory injury, neurological involvement is common in both the acute infection and the post-acute sequelae of SARS-CoV-2 infection (PASC or “long COVID”). Reported manifestations range from mild symptoms such as headache, anosmia and myalgias to

severe complications including stroke, encephalitis, Guillain–Barré syndrome (GBS) and prolonged encephalopathy. Large multicenter cohorts suggest that a majority of hospitalized adults experience at least one neurologic manifestation during their illness. Moreover, a considerable proportion of patients report persistent problems after apparent clinical recovery. Cohort and registry studies estimate that a substantial minority of individuals describe ongoing neurological or neuropsychiatric symptoms—particularly fatigue, cognitive complaints, sleep disturbances and mood changes—for weeks or months after infection, even when the initial disease was mild (1). Both adults and children can be affected, although the patterns, mechanisms and outcomes differ by age.

This narrative review summarizes current evidence on the neurological aspects of COVID-19, focusing on peer-reviewed literature published since 2020. It first outlines the principal pathophysiologic mechanisms by which SARS-CoV-2 affects the nervous system, then reviews acute neurological manifestations in adults and children, long-term sequelae, neuroimaging findings and current therapeutic approaches.

Pathophysiology of COVID-19 in the Nervous System

Direct viral neuroinvasion

SARS-CoV-2 can reach the nervous system, but robust evidence of widespread direct neuronal infection is limited. Viral RNA or protein has been detected in cerebrospinal fluid (CSF) or brain tissue in a subset of patients and at autopsy, particularly in brainstem regions, sometimes accompanied by focal inflammation. These observations confirm that neuroinvasion is possible at least in severe cases (2). However, in vitro models using human neural cultures and brain organoids generally show inefficient infection of neurons compared with non-neuronal cells such as choroid plexus epithelium, suggesting that direct neuronal replication is not the dominant mechanism of injury (3).

Two main routes of central nervous system (CNS) access have been proposed. Hematogenous spread may occur when circulating virus infects endothelial cells of the cerebral vasculature expressing ACE2, disrupting the blood–brain barrier (BBB) and allowing viral particles, inflammatory mediators and immune cells to enter the parenchyma. The choroid plexus and blood–CSF barrier likely represent another point of entry, as ACE2 expression is high in choroid plexus epithelial cells and experimental data show that these cells are permissive to infection (4). A second potential route involves cranial nerves, particularly the olfactory system. Supporting (sustentacular) cells within the olfactory epithelium strongly express ACE2 and are readily infected by SARS-CoV-2, leading to local inflammation, dysfunction of olfactory sensory neurons and transient anosmia. Olfactory neurons themselves have low ACE2 expression, and convincing evidence of axonal transport of virus into the brain in humans is lacking. Overall, current data support a model in which limited neuroinvasion can occur but plays a secondary role compared with systemic and immune-mediated mechanisms (5).

Immune-mediated injury and systemic effects

The predominant contributors to neurologic injury in COVID-19 appear to be indirect mechanisms related to dysregulated host immune responses and the characteristic coagulopathy. Severe infection is associated with a “cytokine storm,” with markedly elevated concentrations of pro-inflammatory

cytokines and chemokines. These mediators increase BBB permeability, activate microglia and astrocytes and can produce toxic encephalopathy or trigger autoimmune responses even when viral burden within the CNS is low. Autopsy series consistently demonstrate microglial activation, microglial nodules and perivascular lymphocytic cuffs in the brains of patients who died with COVID-19, indicating widespread neuroinflammation (6). Post-infectious autoimmune phenomena reported after SARS-CoV-2 infection include ADEM, autoimmune encephalitis and GBS. In GBS, the typical latency of 1–4 weeks between infection and neuropathic symptoms and the presence of antiganglioside antibodies in some patients support a molecular mimicry mechanism similar to that observed after *Campylobacter jejuni* or Zika virus (7).

Coagulopathy and vascular injury

SARS-CoV-2 promotes a prothrombotic state through endothelial dysfunction, platelet activation, the release of procoagulant factors and formation of neutrophil extracellular traps. Hypercoagulability, combined with hypoxia and systemic inflammation, leads to a high incidence of thrombotic complications, including ischemic stroke, venous thromboembolism and microvascular injury. Pathological studies of brain tissue have demonstrated fibrin microthrombi, small infarcts, microhemorrhages and endotheliitis affecting cerebral vessels (8). Diffuse hypoxic–ischemic injury due to severe pneumonia or acute respiratory distress syndrome, shock and prolonged mechanical ventilation further contributes to encephalopathy. These mechanisms often coexist in individual patients, who may experience a mixture of hypoxic injury, inflammatory neurotoxicity, microvascular thrombosis and autoimmune responses, producing a complex clinical picture (9).

Taken together, these pathways help explain the major neurologic phenotypes observed in COVID-19. Systemic inflammation, cytokine and chemokine surges, and blood–brain barrier disruption are closely linked with acute toxic–metabolic encephalopathy and delirium. Endothelial injury, complement activation, and macro- and microvascular thrombosis underlie ischemic stroke, cerebral venous thrombosis, and diffuse white-matter injury. Post-infectious autoimmune responses and molecular mimicry contribute to acute demyelinating syndromes and Guillain–Barré syndrome, whereas chronic immune activation, dysautonomia, and microvascular dysfunction are increasingly implicated in the fatigue, dysautonomia, and cognitive “brain fog” reported in long COVID (21, 34, 35, 50–53).

Acute Neurological Manifestations in Adults

Frequency and spectrum

Neurological involvement is very common in hospitalized adults with COVID-19. The GCS-NeuroCOVID consortium reported that approximately 82% of hospitalized patients developed at least one neurological manifestation, encompassing both self-reported symptoms and clinically diagnosed syndromes. Headache, myalgias, anosmia or ageusia and dizziness are frequent early complaints. Loss of smell or taste, present in roughly one quarter of hospitalized patients in early cohorts and even more common in milder community cases, rapidly became a clinical hallmark of infection (10).

Severe manifestations are concentrated among patients with moderate-to-critical respiratory disease. Acute encephalopathy—defined as delirium, decreased consciousness or other global cognitive

disturbance—occurs in roughly half of hospitalized adults and is strongly associated with disease severity, the need for intensive care and in-hospital mortality (11). Patients typically present with fluctuating confusion, agitation or coma in the context of systemic inflammation, hypoxia, metabolic derangements and heavy sedative exposure, and many show no focal abnormalities on neuroimaging, consistent with toxic-metabolic or hypoxic encephalopathy (12).

Cerebrovascular complications

COVID-19 is associated with an increased risk of both ischemic and hemorrhagic stroke. Across hospitalized cohorts, 1–6% of patients experience an acute ischemic stroke during their illness, often involving large-vessel occlusions and multi-territory infarcts that reflect hypercoagulability and endothelial injury rather than classic atherosclerosis. Cerebral venous sinus thrombosis, although rare in absolute terms, has been described in association with SARS-CoV-2 infection and in very rare cases after adenoviral vector vaccination (13). Intracerebral hemorrhage and cerebral microbleeds occur as a consequence of coagulopathy, thrombocytopenia, anticoagulant therapy and vascular damage. In critically ill patients, particularly those with ARDS and prolonged ventilation, MRI frequently reveals scattered microhemorrhages in the white matter and corpus callosum together with features of diffuse leukoencephalopathy. These abnormalities correlate with severe hypoxia and critical illness and are associated with poorer functional outcomes and higher mortality (14).

Inflammatory CNS syndromes

SARS-CoV-2–associated meningitis or encephalitis, in which the virus is detected in CSF or brain, is rare but documented. More commonly, patients develop encephalitis patterns thought to be immune-mediated rather than due to direct viral replication. Cases of acute necrotizing encephalopathy, characterized by hemorrhagic lesions of the thalami and other deep structures, have been described in association with profound cytokine storm and resemble similar phenomena seen in influenza. ADEM and other demyelinating syndromes, including autoimmune encephalitides such as anti-NMDA receptor encephalitis, have also been reported in adults and adolescents after COVID-19, usually with multifocal white matter lesions on MRI and good response to corticosteroids or intravenous immunoglobulin (15).

Seizures and movement disorders

New-onset seizures in COVID-19 usually occur in the context of severe systemic illness, metabolic derangement, stroke or encephalitis. Status epilepticus has been described but remains uncommon. Pre-existing epilepsy may be destabilized by fever, systemic inflammation and drug interactions. Transient movement disorders of varying types, including myoclonus, asterixis and parkinsonian features, have been observed in association with encephalopathy. A causal link between SARS-CoV-2 infection and long-term neurodegenerative parkinsonism remains speculative and unproven (16).

Peripheral nervous system involvement

GBS is the best-characterized peripheral nervous system complication of COVID-19. Systematic reviews identify numerous cases temporally associated with SARS-CoV-2 infection, with clinical and electrophysiologic features similar to classic post-infectious GBS. Most patients respond to IVIG or plasmapheresis, although some require prolonged ventilatory support and intensive rehabilitation. Variants such as Miller Fisher syndrome and facial diplegia have also been reported (17).

Other peripheral manifestations include cranial neuropathies such as Bell's palsy, myositis with myalgia and raised creatine kinase, critical illness neuromyopathy and, rarely, fulminant rhabdomyolysis. Anecdotal reports of audiovestibular symptoms, including sudden sensorineural hearing loss and vestibular neuritis, have been linked temporally to SARS-CoV-2, but clear epidemiologic associations are still being examined.

In summary, adult patients with acute COVID-19 experience a broad spectrum of neurological problems. The most frequent issues are headache, anosmia or ageusia, encephalopathy and cerebrovascular events, while meningitis or encephalitis, GBS and seizures are less common but clinically significant. The presence of severe neurological manifestations often portends a worse prognosis and underscores the need for vigilant neurological monitoring in hospitalized patients (18).

Neurological Manifestations in the Pediatric Population

Children and adolescents generally have less severe respiratory disease than adults, yet neurological complications occur in both acute infection and in post-infectious MIS-C. In the pediatric GCS-NeuroCOVID cohort, 44% of hospitalized children with acute COVID-19 or MIS-C had at least one neurological manifestation. Roughly 40% of those with acute infection and two-thirds of those with MIS-C exhibited neurological symptoms, indicating that systemic inflammation in MIS-C is associated with a higher risk of neuroinvolvement (19).

Acute COVID-19 in children

Among children hospitalized with acute SARS-CoV-2 infection (without MIS-C), headache, encephalopathy, seizures and weakness are the predominant neurological presentations. Headache is reported in around one sixth of patients and may present as irritability in younger children. Acute encephalopathy or altered mental status occurs in approximately 10–15% and can range from confusion and lethargy to coma in severe cases. Other mild manifestations include dizziness, ataxia and loss of smell or taste, although anosmia is difficult to elicit in younger age groups. Ischemic and hemorrhagic stroke are rare but documented in pediatric COVID-19, sometimes in association with congenital heart disease, vasculopathy or pre-existing prothrombotic conditions (20).

MIS-C and post-infectious complications

MIS-C typically emerges 2–6 weeks after acute SARS-CoV-2 infection and is characterized by high fever, marked inflammation and multi-organ dysfunction. Neurologic involvement is frequent. Cohorts report that between one fifth and two thirds of children with MIS-C develop headache, encephalopathy, seizures, meningeal signs or focal deficits. Most of these symptoms are mild and transient, but severe complications have been described. These include encephalitis, ADEM-like demyelination, cytotoxic lesions of the corpus callosum, cerebral edema, pseudotumor cerebri and ischemic or hemorrhagic stroke. Neuroimaging in MIS-C often shows reversible splenial lesions, white matter changes or findings consistent with PRES; these abnormalities usually improve with immunomodulatory treatment (21).

Outcomes and sequelae

Overall mortality from pediatric neuro-COVID is low, but children who develop severe neurologic complications are at increased risk of residual deficits. In international cohorts, severe neurological

manifestations such as coma, prolonged seizures or stroke during acute infection or MIS-C roughly double the risk of new neurocognitive or functional morbidity at discharge compared with children without such complications (22). These deficits may include impaired school performance, behavioral changes, motor weakness or difficulties with activities of daily living, often necessitating physical, occupational or speech therapy. Encouragingly, many affected children improve substantially over subsequent months, reflecting the plasticity of the developing nervous system (23).

In summary, children with COVID-19 exhibit neurological symptoms ranging from common mild issues like headache and febrile seizures to rare but serious syndromes such as encephalitis, stroke and GBS. MIS-C, a hyperinflammatory post-infectious condition, frequently involves the nervous system and can lead to encephalopathy or demyelination. Prompt recognition, early involvement of pediatric neurology and careful long-term follow-up are crucial (24).

Long-Term Neurological Sequelae (Long COVID)

A significant proportion of individuals recovering from COVID-19 experience symptoms that persist or newly appear beyond four to twelve weeks after onset. When these symptoms are prolonged and cannot be explained by alternative diagnoses, they are collectively termed long COVID or PASC. Neurological and neuropsychiatric complaints are particularly prominent and often disabling (25). However, defining and diagnosing long COVID remains challenging. Case definitions from organizations such as the WHO, CDC, and NICE differ slightly in required symptom duration and proof of infection, which complicates comparison across studies. Many of the core complaints—fatigue, poor concentration, headache, sleep disturbance, and mood changes—are non-specific and overlap with the consequences of critical illness, social isolation, and pandemic-related stressors. In children, diagnostic uncertainty is even greater because somatic symptoms are common, developmental stage influences symptom reporting, and school or family stress may mimic or exacerbate post-COVID complaints. A careful history, stepwise evaluation to exclude alternative diagnoses, and longitudinal follow-up are therefore essential when diagnosing long COVID in both adults and children (7, 34, 35).

Cognitive impairment and “brain fog”

Perhaps the hallmark of neuro-long COVID in adults is the experience of cognitive impairment or “brain fog”. Patients describe slowed thinking, impaired concentration, difficulties with memory and word-finding and reduced multitasking capacity. Many also report mental fatigue and reduced processing speed even in routine activities. Formal neuropsychological testing confirms deficits in attention, executive function and memory in a substantial fraction of survivors, including individuals whose acute illness was mild and did not require hospitalization(26, 27).

Longitudinal evidence from the UK Biobank, where participants underwent brain MRI before and after infection, demonstrated that even predominantly mild SARS-CoV-2 infections were associated with greater loss of gray matter in olfactory-related and limbic regions and with modest decline in cognitive test performance compared with matched uninfected controls. These observations suggest that subtle structural brain changes may underlie persistent cognitive symptoms, though the reversibility of such changes remains uncertain (2, 28).

Fatigue, sleep disorders and dysautonomia

Chronic fatigue is one of the most disabling long-term manifestations. Patients often experience a combination of physical and mental exhaustion that worsens after exertion, resembling post-exertional malaise in myalgic encephalomyelitis or chronic fatigue syndrome. Sleep disturbances are also common; surveys and cohort studies indicate that approximately 20–30% of long COVID patients develop persistent insomnia, fragmented sleep or altered circadian rhythm, with a higher incidence than observed after influenza or other acute illnesses. Polysomnography shows disruption of normal sleep architecture, including reduced restorative slow-wave and REM sleep (23, 29).

Dysautonomia has emerged as another important contributor to long-term symptoms. Postural orthostatic tachycardia syndrome, orthostatic intolerance and labile blood pressure are increasingly recognized in long COVID clinics. Patients, often young adults, report palpitations, lightheadedness, exercise intolerance and cognitive clouding when upright. Observational data indicate that the risk of new-onset peripheral and autonomic neuropathies is higher after COVID-19 than after other respiratory infections, supporting a link between SARS-CoV-2 and autonomic nervous system injury (30).

Neuropsychiatric manifestations

The burden of mood and anxiety disorders following COVID-19 is substantial. Large electronic health record studies involving hundreds of thousands of survivors show that approximately one third receive a neurologic or psychiatric diagnosis within six months of infection, including mood disorders, anxiety disorders, insomnia and cognitive impairment. A substantial minority—around 4–8%—receive a first-time diagnosis of depression or anxiety (7, 31). The risk is highest among patients who required intensive care or developed encephalopathy during the acute illness. Symptomatically, survivors frequently report depressed mood, anhedonia, irritability, generalized anxiety, panic attacks and features of post-traumatic stress disorder. These conditions derive from an interplay of direct neurobiological effects of infection, systemic inflammation, the psychological trauma of severe illness and the broader social consequences of the pandemic (32).

Other persistent neurological symptoms

Several other neurological complaints have been documented in long COVID cohorts. Chronic daily headaches, often with migraine-like features, can persist for months in patients with or without prior headache history. Many individuals report paresthesias, burning pain, allodynia or restless legs. In some, small-fiber neuropathy has been confirmed by skin biopsy. Persistent olfactory and gustatory dysfunction is common; whereas most people recover within weeks, a subset experiences hyposmia, dysgeusia or parosmia for many months (33). Tinnitus and subjective hearing difficulties are also described. Evidence that COVID-19 increases long-term risk of classical neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease is currently limited and conflicting, and definitive conclusions await longer follow-up (14).

Long COVID in children

Children and adolescents can develop long COVID, although prevalence estimates are lower than in adults and vary widely across studies because of differences in design and control groups. Common pediatric symptoms include fatigue, headache, impaired concentration, sleep disturbances, mood

swings and changes in behavior. School-aged children may present with reduced academic performance, difficulty paying attention in class or irritability. Many of these complaints are also common in the general pediatric population and may be influenced by pandemic-related stressors, so careful assessment is necessary to attribute them to SARS-CoV-2. Nonetheless, pediatric long COVID clinics report adolescents with a syndrome strikingly similar to that in adults, characterized by chronic headache, cognitive fatigue, exercise intolerance and autonomic complaints (34).

Most longitudinal pediatric cohorts are reassuring: the majority of children show gradual improvement, and only a small fraction have persistent disabling symptoms at one year. Those at higher risk for long-lasting problems include teenagers and children who experienced MIS-C or required hospitalization during the acute illness. MIS-C survivors who had significant neurologic involvement may require extended rehabilitation, but serious permanent disability appears uncommon with appropriate care (35).

Proposed mechanisms of neuro-long COVID

Several mechanistic hypotheses have been proposed to explain neuro-long COVID. Persistent immune activation with elevated pro-inflammatory cytokines, microglial activation, and blood–brain barrier disruption may drive chronic neuroinflammation. Microvascular dysfunction and a prothrombotic state with diffuse microthrombi could impair cerebral perfusion and oxygen delivery. Autoimmune phenomena, including the generation of autoreactive T cells and autoantibodies against neuronal or autonomic targets, may contribute to small-fiber neuropathy, dysautonomia, and other post-infectious syndromes. Viral persistence in tissue reservoirs and reactivation of latent viruses have also been suggested. These mechanisms are not mutually exclusive and likely differ in prominence across patients, helping to explain the heterogeneous constellation of fatigue, cognitive complaints, sleep disturbance, and mood symptoms reported in long COVID (21, 34, 35, 50–53).

Neuroimaging Findings in COVID-19

Imaging in acute disease

Neuroimaging in acutely ill patients mirrors the observed neurological complications. CT and MRI frequently demonstrate acute ischemic infarcts—often large-vessel occlusions with extensive thrombus—and intracranial hemorrhages, including lobar hemorrhage, subarachnoid hemorrhage and numerous microbleeds. In critically ill patients with prolonged coma, MRI commonly shows diffuse leukoencephalopathy and cerebral microhemorrhages, particularly in the subcortical and periventricular white matter and the corpus callosum. These findings have been linked to severe hypoxia, high ventilatory pressures and systemic inflammation and correlate with worse neurological outcomes (37). Other patterns include PRES, characterized by vasogenic edema predominantly in the parietal and occipital white matter, and cytotoxic lesions of the corpus callosum, usually manifesting as transient restricted diffusion in the splenium. Cerebral venous sinus thrombosis and its parenchymal consequences are identified in a minority of cases. Inflammatory involvement of the CNS may appear as mesial temporal or multifocal cortical T2/FLAIR hyperintensities, leptomeningeal enhancement or diffuse cortical swelling, though many encephalopathic patients show normal structural imaging (38).

A meta-analysis of MRI findings in COVID-19 reported abnormalities in about 55% of imaged patients. Perfusion and susceptibility-weighted changes—reflecting microvascular injury and microbleeding—were particularly prevalent, followed by white matter lesions, acute infarcts, leptomeningeal enhancement and FLAIR signal abnormalities. These imaging patterns underscore the importance of vascular and inflammatory mechanisms in COVID-19-related brain injury (39).

Imaging in MIS-C and pediatric patients

Most children with acute COVID-19 or MIS-C who undergo neuroimaging have normal studies. When abnormalities are present, they commonly include reversible splenic lesions of the corpus callosum, white matter changes resembling ADEM, PRES, cerebral edema or, rarely, ischemic or hemorrhagic stroke. In MIS-C, these radiologic abnormalities usually resolve over weeks to months and parallel clinical improvement after immunomodulatory therapy, highlighting the largely reversible nature of pediatric neuro-COVID in many cases (40).

Imaging in long COVID

In patients presenting with long COVID symptoms such as brain fog or chronic headache, standard structural MRI and CT are often unremarkable. This normal imaging can be frustrating for patients seeking tangible evidence of their impairments. Research-oriented imaging, however, has revealed more subtle abnormalities (40). The UK Biobank study demonstrated accelerated cortical thinning and gray matter loss in olfactory-related and limbic regions in individuals scanned before and after SARS-CoV-2 infection compared with controls. Small FDG-PET case series in long COVID patients have shown hypometabolism in frontal cortex, basal ganglia, temporal lobes and brainstem, even when structural MRI was normal. Functional MRI studies suggest altered connectivity within attention and executive networks. Transcranial Doppler and other non-invasive measures indicate lingering changes in cerebrovascular reactivity in some survivors. These findings support an organic basis for chronic cognitive and neuropsychiatric symptoms, although they are not yet widely used for routine clinical decision-making (23, 41).

Treatment Strategies for Neurological Complications

Acute phase management

Optimal management of systemic COVID-19 is the foundation of preventing and mitigating neurological injury. Early use of antiviral agents such as remdesivir in hospitalized patients and nirmatrelvir/ritonavir in high-risk outpatients reduces progression to severe disease and may indirectly lower the risk of neurocomplications by attenuating viral replication. In hypoxic patients with evidence of pneumonia or ARDS, systemic corticosteroids, particularly dexamethasone, have become standard of care and improve survival by damping excessive inflammation (42). Thromboprophylaxis with low-molecular-weight heparin is routinely employed in hospitalized patients to counteract COVID-associated coagulopathy, and intermediate- or full-dose anticoagulation is considered in selected high-risk individuals. Careful attention to oxygenation, hemodynamic stability, glycemic control and avoidance of unnecessary sedatives is essential to minimize hypoxic and metabolic encephalopathy (43). In addition, when antiviral regimens such as nirmatrelvir/ritonavir are used, clinicians should carefully review patients' concomitant neurologic medications for potential drug-drug interactions and consult up-to-date interaction resources or

clinical pharmacists before co-prescribing these agents.

For specific neurological emergencies, standard evidence-based protocols should be followed regardless of COVID status. Patients with acute ischemic stroke who meet criteria for intravenous thrombolysis or mechanical thrombectomy should receive these therapies with appropriate infection-control precautions, as timely reperfusion can be life- and brain-saving. Secondary prevention with antiplatelet agents or anticoagulants is tailored to each patient's thrombotic and hemorrhagic risk profile. Intracerebral hemorrhage is managed with blood pressure control, reversal of coagulopathy and neurosurgical consultation when indicated (44). Seizures and status epilepticus are treated with benzodiazepines and second-line antiseizure medications such as levetiracetam according to established protocols; there is no evidence that COVID-related seizures require special regimens. Encephalopathy and delirium are addressed by treating underlying systemic factors, reducing sedative exposure, implementing non-pharmacologic delirium prevention strategies and using low-dose antipsychotics only when necessary for severe agitation (45).

Immune-mediated syndromes and MIS-C

Immune-mediated neurological syndromes associated with COVID-19 are treated similarly to their non-COVID counterparts. GBS is managed with IVIG or plasmapheresis, both of which shorten time to recovery. ADEM, autoimmune encephalitis and transverse myelitis are treated with high-dose intravenous corticosteroids, often followed by an oral taper, and in some cases with adjunctive IVIG or plasmapheresis. Early recognition and initiation of immunotherapy are associated with better outcomes (46).

Management of MIS-C focuses on immunomodulation and supportive care. Current protocols generally recommend IVIG and systemic corticosteroids as first-line therapy, with addition of biologic agents such as anakinra or infliximab in refractory cases. Neurologic manifestations, including encephalopathy, headaches, seizures and demyelinating lesions, frequently improve as the systemic inflammatory syndrome resolves. Specific complications such as stroke, intracranial hypertension or seizures require targeted treatment alongside MIS-C therapy (47).

Symptomatic and supportive therapy

Beyond disease-modifying interventions, many neurological symptoms require symptomatic management and rehabilitation. Headache during acute infection is treated with analgesics and, when appropriate, migraine-specific therapies. For anosmia or hyposmia, olfactory training—repeated exposure to a panel of odors over weeks—has shown benefit and is widely recommended, although pharmacologic treatments remain unproven. Patients with significant motor, cognitive or speech deficits after stroke, GBS or critical illness benefit from early and intensive rehabilitation delivered by multidisciplinary teams (48).

Management of long-term neurological sequelae

At present there is no single therapy that reliably reverses long COVID, and care is individualized. A comprehensive, multidisciplinary approach is recommended. Rehabilitation is central: cognitive rehabilitation therapies use structured exercises and compensatory strategies to improve attention, memory and executive function, whereas graded physical therapy aims to restore strength and endurance. In patients with post-exertional symptom exacerbation, activity is increased very

gradually with careful pacing to avoid symptom flares. Occupational therapy helps patients adapt to residual limitations in daily living and work (49).

Symptom-directed pharmacotherapy is commonly employed. Persistent insomnia is managed with sleep-hygiene measures, melatonin and, when needed, low-dose sedating antidepressants such as trazodone or amitriptyline. Chronic headaches are treated according to standard paradigms for migraine or tension-type headache, including acute therapies (for example, triptans) and preventive medications when attacks are frequent. Neuropathic pain and paresthesias can respond to gabapentin, pregabalin, duloxetine or similar agents. In severe cases of cognitive fatigue and daytime somnolence, some clinicians have tried stimulants such as methylphenidate or wake-promoting agents like modafinil, although controlled trial data are still limited (50). For agents such as methylphenidate or modafinil, the current evidence base consists mainly of small case series and uncontrolled observational reports; randomized controlled trials are lacking, and these drugs should therefore be used cautiously and on an individualized basis (50–53). Management of dysautonomia includes non-pharmacologic strategies—such as increased fluid and salt intake, use of compression stockings and physical counter-maneuvers—and pharmacologic measures including low-dose beta-blockers to control tachycardia, ivabradine in selected cases and midodrine for orthostatic hypotension (51). Neuropsychiatric care is integral. Many patients benefit from psychological counseling, cognitive-behavioral therapy and, where appropriate, pharmacologic treatment of depression, anxiety or post-traumatic stress disorder with selective serotonin reuptake inhibitors or other agents. Addressing mental health often improves sleep, fatigue and perceived cognitive inefficiency (52). Several investigational approaches seek to target proposed mechanisms of long COVID. Low-dose naltrexone, antihistamines aimed at mast-cell activation, IVIG for suspected autoimmune neuropathy and extended anticoagulation or antiplatelet therapy for microclots are being explored in small studies and clinical trials. At present, evidence for their routine use is insufficient, and they should generally be considered only within research settings or under specialist supervision. Large initiatives such as the NIH RECOVER program are evaluating antivirals, immunomodulators, metabolic therapies and rehabilitation strategies to define effective treatments (53). For other proposed treatments, including low-dose naltrexone and various immunomodulatory regimens, evidence is likewise emerging but remains preliminary, and routine use outside of clinical trials or specialist supervision is not currently supported (50–53). In children with long COVID, reassurance and monitoring are often sufficient, as many symptoms resolve spontaneously over time. When concentration difficulties, mood changes or autonomic symptoms significantly interfere with school or daily life, referral to pediatric neurology, cardiology or psychology is recommended. Treatment principles largely mirror those in adults but must be tailored to developmental stage and family context.

Conclusion

COVID-19 has profound implications for the nervous system across the lifespan. In adults, acute infection is frequently accompanied by neurological symptoms and syndromes, ranging from anosmia and headache to encephalopathy, stroke and GBS. Such complications substantially increase morbidity and mortality, particularly in patients with severe respiratory disease. Children, although less likely to develop critical pneumonia, can experience meaningful neurologic morbidity in the context of acute infection and especially MIS-C, where intense systemic inflammation predisposes to encephalopathy, demyelination and, rarely, stroke.

Beyond the acute phase, a substantial subset of survivors grapples with lingering neurological and neuropsychiatric symptoms. The constellation of cognitive impairment, fatigue, sleep disturbance, dysautonomia and mood disorders that characterizes long COVID can markedly impair quality of life and ability to work or attend school, even when standard imaging and laboratory tests are normal. Emerging evidence from imaging and immunological studies supports an organic basis for these complaints, implicating persistent inflammation, endothelial dysfunction, microvascular injury, autoimmunity and possibly viral persistence. Clinicians should maintain a high index of suspicion for acute neurological complications of COVID-19 and promptly involve neurology services. Standard evidence-based treatments, such as reperfusion therapy for stroke and immunotherapy for GBS, should be applied without undue delay in patients with SARS-CoV-2 infection. Long-term management requires multidisciplinary rehabilitation, symptom-targeted pharmacotherapy and psychological support. Dedicated long COVID clinics that integrate neurology, cardiology, rehabilitation and mental health services offer a promising model for comprehensive care. As the pandemic transitions into an endemic phase, the neurologic sequelae of SARS-CoV-2 will remain a major challenge. Continued surveillance, longitudinal cohort studies and randomized clinical trials are needed to clarify long-term risks, including potential acceleration of neurodegenerative diseases, and to identify effective preventive and therapeutic strategies. The insights gained from studying neuro-COVID are likely to enrich our understanding of other viral and post-infectious neurological disorders, highlighting the complex interplay between viral pathogens, immune responses, vascular health and brain function. The authors declare no financial conflicts of interest related to this work. One author (A.A.) is a co-author on several of the cited articles; these studies are referenced alongside the broader literature to illustrate specific clinical and imaging observations.

Conflict of interest

The authors declared no conflict of interest.

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