COVID-19 Infection: A Neuropsychiatric Perspective

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As a potentially life-threatening disease with no definitive treatment and without fully implemented population-wide vaccination, COVID-19 has created unprecedented turmoil in socioeconomic life worldwide. In addition to physical signs from the respiratory and many other systems, the SARS-CoV-2 virus produces a broad range of neurological and neuropsychiatric problems, including olfactory and gustatory impairments, encephalopathy and delirium, stroke and neuromuscular complications, stress reactions, and psychoses. Moreover, the psychosocial impact of the pandemic and its indirect effects on neuropsychiatric health in noninfected individuals in the general public and among health care workers are similarly far-ranging. In addition to acute neuropsychiatric manifestations, COVID-19 may also produce late neuropsychiatric sequelae as a function of the psychoneuroimmunological cascade that it provokes. The present article presents a state-of-the-science review of these issues through an integrative review and synthesis of case series, large-cohort studies, and relevant meta-analyses. Heuristics for evaluation and further study of the neuropsychiatric manifestations of SARS-CoV-2 infection are offered.

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The coronavirus 2019 disease (COVID-19) pandemic produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has disrupted all aspects of life, produced severe adverse socioeconomic burdens, and imposed marked psychosocial stress on people all around the world (1–4). Although best known for its severe effects on respiratory function, SARS-CoV-2 produces a broad range of acute and chronic neurological and neuropsychiatric problems (4). There is emerging evidence that SARS-CoV-2 enters the CNS through olfactory or circulatory routes, where it produces direct adverse effects on neurological and neuropsychiatric health; systemic infection with SARS-CoV-2 produces indirect negative effects on the CNS mediated by cytokines and delayed immune-mediated processes (5). Through these mechanisms, acute infection with SARS-CoV-2 produces acute stroke, neuromuscular dysfunction, demyelinating disorders, encephalopathy, emotional disturbances, and psychosis in a substantial proportion of infected individuals and may engender chronic and late-onset complications among those who survive acute infection (6, 7).

A large meta-analysis of 72 studies comprising 3,559 patients with suspected or confirmed SARS coronavirus, Middle East respiratory syndrome (MERS) coronavirus, or SARS-CoV-2, indicated that during the acute illness, common neuropsychiatric symptoms included confusion, depressed mood, anxiety, impaired memory, and insomnia (8). Data for COVID-19 patients indicated that there was a high rate of delirium, particularly in intensive care unit (ICU) patients (65%−69%). Another meta-analysis of 41 studies indicated that the most common specific neurological symptoms in COVID-19 patients included olfactory (35.7%−85.6%) and gustatory (33.3%−88.8%) disorders, especially in mild cases; Guillain-Barré syndrome (GBS) and acute inflammation of the brain, spinal cord, and meninges were repeatedly reported after COVID-19 (9). A meta-analysis of 31 studies assessing the mental health status in COVID-19 patients (N=5,153) found a 45% pooled prevalence of depression, 47% pooled prevalence of anxiety, and 34% pooled prevalence of sleeping disturbances (10). A recent national surveillance study in the United Kingdom reporting on the neurological and neuropsychiatric complications of COVID-19 in 125 patients indicated that 77 (62%) presented with a stroke, of whom 57 (74%) had an ischemic stroke, nine (12%) an intracerebral hemorrhage, and one (1%) CNS vasculitis (11). A total of 39 (31%) patients presented with altered mental status; nine (23%) had unspecified encephalopathy, and seven (18%) had encephalitis; the remaining 23 (59%) patients with altered mental status fulfilled criteria for psychiatric diagnoses, including new-onset psychosis (n=10), neurocognitive (dementia-like) syndrome (n=6), and affective disorder (n=4).

Thus, both neurological and neuropsychiatric health are affected by SARS-CoV-2 infection. The COVID-19 pandemic has also had an important impact on the mental health of many individuals in the general population as a result of

loss of loved ones, fear of calamity or death, financial hardships, social isolation resulting from government-mandated quarantine and social distancing requirements, and major disruptions of daily life and social connectedness (12, 13). Health professionals have experienced higher levels of negative psychological effects of the COVID-19 pandemic, with emotional trauma associated with the provision of care in conditions analogous to combat experiences, sometimes exceeding psychological tolerances and the capacity for adapting or coping (14, 15). All these issues are herein reviewed, data from meta-analyses are tabulated, and etiopathogenetic mechanisms are pictorially illustrated.

CNS MANIFESTATIONS OF COVID-19

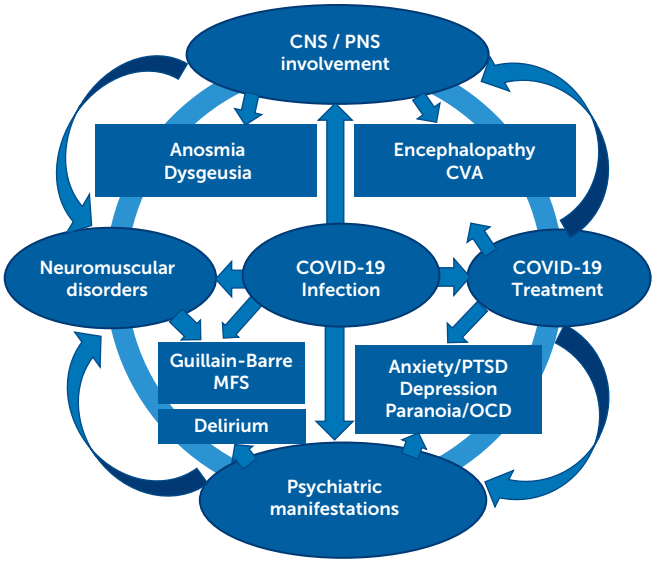
Neurological Manifestations

The SARS-CoV-2 virus appears to spread from the respiratory system to the CNS using transneuronal and hematogenous mechanisms (5, 16). Neurological manifestations may vary from mild (such as taste and smell dysfunction, dizziness, headache, altered consciousness) to severe (e.g., ischemic stroke, encephalitis, encephalopathy) (17, 18). SARS-CoV-2 infection may lead to neurological and psychiatric manifestations, including indirect processes resulting from thrombotic complication, inflammatory consequences, hypoxia or hemodynamic perturbations, and direct infection and involvement of the CNS due to the neurotropic properties of the virus, virus-induced hyperinflammatory and hypercoagulable states, and postinfectious immune-mediated processes (17, 19, 20). A wide spectrum of neurologic manifestations of SARS-CoV-2 infection has been reported, including encephalopathy, encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic and hemorrhagic stroke, venous sinus thrombosis, and endothelialitis (18, 21–23) (Figure 1). In the peripheral nervous system (PNS), SARS-CoV-2 infection is associated with anosmia and hypogeusia, neuromuscular disorders, and GBS (19).

A recent Italian study of 1,760 COVID-19 patients reported that 137 patients developed neurologic manifestations; they appeared after COVID-19 symptoms in 98 patients and were the presenting symptom in 39 patients (24). Neurological manifestations included cerebrovascular disease (38.7%), comprising 37 ischemic strokes and 11 hemorrhagic strokes, four transient ischemic attacks, one cerebral venous thrombosis; PNS disorders (22.6%), including 17 GBS; altered mental status (35.8%), including one necrotizing encephalitis and two cases with detection of SARS-CoV-2 RNA in the CSF; and various other disorders, such as myelopathy associated with anti-SARS-CoV-2 antibodies in the CSF in two patients.

Among 509 hospitalized COVID-19 patients in the United States, neurologic manifestations were detected in 215 (42.2%) at disease onset, in 319 (62.7%) upon hospitalization, and in 419 (82.3%) during the course of the disease (25). Neurologic symptoms included myalgia (44.8%), headache (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%), and anosmia (11.4%). Severe COVID-19 (odds ratio=4.02; p<0.001) and younger age (odds ratio=0.982; p=0.014) were risk factors for neurological symptoms. The majority (71%) of patients had a favorable functional outcome at discharge. Encephalopathy was an independent predictor of worse functional outcome (odds ratio=0.22; p<0.001) and higher 30-day mortality (21.7% versus 3.2%; p<0.001).

FIGURE 1. Spectrum of neurological and psychiatric manifestations produced by COVID-19 infection[a]



[a] CNS=central nervous system; CVA=cerebrovascular accident; MFS=Miller-Fisher syndrome; OCD=obsessive-compulsive disorder; PNS=peripheral nervous system; PTSD=posttraumatic stress disorder.

Anosmia and ageusia. A meta-analysis of 24 studies comprising 8,438 patients with COVID-19 infection indicated a high prevalence of anosmia (41%) and ageusia (38.2%) (26). Increasing mean age correlated with lower prevalence of anosmia (coefficient=−0.076; p=0.02) and ageusia (coefficient=−0.073; p=0.03) (26). There was a higher prevalence of anosmia with the use of objective measurements compared with self-reports (coefficient=2.33; p=0.01). No significant influence of the prevalence of anosmia or ageusia by sex was observed.

Multiple possible mechanisms have been suggested for the development of anosmia in COVID-19, including olfactory cleft syndrome, postviral anosmia syndrome, cytokine storm, direct damage of olfactory sensory neurons, and impairment of the olfactory perception center in the brain (27).

Stroke. A recent retrospective multicenter cohort study from China enrolling 917 COVID-19 patients (mean age=48.7 years [SD=17.1], 55% male) indicated that the frequency of new-onset critical neurologic events was 3.5% (n=32/917) overall and 9.4% (n=30/319) among those with severe or critical COVID-19; these events were impaired consciousness (n=25) or stroke (n=10) (28). According to a recent case series of 16 patients with ischemic stroke related to

COVID-19, ischemic events presented as small vessel occlusions, branch emboli, or large vessel occlusions (29). The most common etiology was cryptogenic. Patients with large vessel occlusions tended to be younger and male and had elevated acute inflammatory markers. Another case series of 22 patients (mean age=59.5 years [SD=16.0]; females, n=12) with diagnosed COVID-19 and acute cerebrovascular pathologies included 17 cases of acute ischemic stroke, three cases of aneurysm rupture, and two cases of sinus thrombosis (30). Of the stroke and sinus thrombosis patients, 16 (84.2%) underwent a mechanical thrombectomy procedure. A favorable thrombolysis in cerebral infarction score was achieved in all patients. Of the 16 patients who underwent a mechanical thrombectomy, five (31.3%) succumbed. Of all patients (N=22), three (13.6%) developed hemorrhagic conversion requiring decompressive surgery; 11 (50%) patients had a poor functional status (modified Rankin score, 3–6) at discharge, and the total mortality incidence was 8/22 (36.4%). The authors concluded that despite timely intervention and favorable reperfusion, the mortality rate in COVID-19 patients with large vessel occlusion was high. This group was characterized by younger age, involvement of both the arterial and venous vasculature, multivessel involvement, and complicated procedures due to the clot consistency and burden.

According to a multicenter, multinational observational study among 17,799 COVID-19 patients, stroke occurred in 156 (0.9%): 123 (79%) were ischemic, 27 (17%) were intracerebral/subarachnoid hemorrhages, and six (4%) were cerebral sinus thromboses (31). Subsequent stroke risks calculated with meta-analyses under low to moderate heterogeneity were 0.5% among all centers in all countries and 0.7% among countries with higher health expenditures. The need for mechanical ventilation (odds ratio=1.9, p=0.03) and the presence of ischemic heart disease (odds ratio=2.5, p=0.006) were predictive of stroke.

A recent report from Italy on 1,760 COVID-19 patients indicated that 137 developed neurologic manifestations; in 98 patients, neurological manifestations appeared after other COVID-19 symptoms, whereas neurological manifestations were the presenting symptoms in 39 patients (24). Neurological manifestations included, among others, cerebrovascular disease (38.7%), comprising 37 ischemic and 11 hemorrhagic strokes; four transient ischemic attacks; and one cerebral venous thrombosis. A recent U.K.-wide surveillance report on the neurological and neuropsychiatric complications of COVID-19 in 125 patients showed that 77 (62%) patients presented with stroke, of whom 57 (74%) suffered an ischemic stroke, nine (12%) an intracerebral hemorrhage, and one (1%) CNS vasculitis (11).

Epilepsy. A recent study of 30 patients with diagnosis of epilepsy and COVID-19 indicated that 13 patients (43.4%) had new-onset epileptic seizure without epilepsy history; these patients suffered more severe or critical COVID-19, which led to a worse prognosis (32). It has been suggested that a severe COVID-19 disease course and advanced disease stages can result in hypoxic encephalopathy, cerebrovascular events, and cytokine storm, which may trigger the development of acute seizures (33). It has also been suggested that proinflammatory cytokines can cause blood-brain barrier disruption, increase glutamate and aspartate and reduce GABA levels, impair the function of ion channels, and thus lead to an increase in neuronal excitability with consequent epilepsy (34). On the other hand, secondary seizure is a well-known consequence of stroke, electrolyte and metabolic imbalance, hypoxia, fever, increased oxidative stress, and mitochondrial dysfunction in general; the occurrence of such seizures among persons with COVID-19 therefore may not be directly related to this condition.

Indeed, another study from China enrolling 304 people with COVID-19 (of whom 108 had severe illness and none had a known history of epilepsy), neither acute symptomatic seizures nor status epilepticus were observed (35). Two people had seizure-like symptoms during hospitalization due to acute stress reaction and hypocalcemia; 84 (27%) had brain insults or metabolic imbalances during the disease course known to increase the risk of seizures, albeit with no occurring seizures. The authors concluded that there was no evidence for increased risk of seizures in patients with COVID-19.

GBS and other neuromuscular disorders. A recent review of seven studies reported 11 cases of GBS (acute idiopathic polyneuritis; mean age=61.54 years [SD=14.18]) developing at a mean of 8 days (36). Among nine of 11 patients undergoing lumbar puncture, albuminocytological dissociation on CSF analysis was found in eight patients while normal protein and no cells was observed in only one patient. Two patients had MRI evidence of caudal nerve root enhancement, while one patient had bilateral facial nerve enhancement. Among 10 out of 11 patients who had an electrodiagnostic study, six patients had demyelinating patterns. Three patients had acute sensory motor axonal neuropathy, and one had acute motor axonal neuropathy. All 11 patients received intravenous immunoglobulin in combination with antivirals, antibiotics, and immunosuppressive agents. One patient succumbed to the disease. Persistence or worsening of symptoms was reported in two patients. One patient had complete neurological recovery, while the other four patients had improvement of symptoms with decreased weakness. One patient had hemodynamic changes with severe drug-resistant hypertension, suggesting possible autonomic nervous system involvement. Four out of 11 patients developed neuromuscular respiratory failure. One patient developed respiratory failure 3 days from the onset of neurological symptoms, one at 2 weeks, and two at 1 month after onset of neurological symptoms.

Another recent report included 42 patients with GBS associated with SARS-CoV-2 infection (37). Median time between COVID-19 and GBS onset in 36 patients was 11.5 days (interquartile range, 7.7–16). The most common clinical features were limb weakness (76.2%), hyporeflexia (80.9%), sensory disturbances (66.7%), and facial palsy (38.1%). Dysautonomia occurred in 19% and respiratory failure in 33.3%; 40.5% of

patients were admitted in the ICU. Electrodiagnosis was demyelinating in 80.5%. Treatment included intravenous immunoglobulin or plasma exchange (92.8%) with definite improvement or recovery at short-term follow-up in 62.1% of patients.

A review of 14 papers reporting 18 patients with GBS associated with COVID-19 indicated that the interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from −8 to 24 days (mean=9 days; median=10 days) (38). Most of the patients had a typical GBS clinical form predominantly with a demyelinating electrophysiological subtype. Mechanical ventilation was necessary in eight (44%) patients. Two (11%) patients died. Another review of 62 COVID-19 patients with polyradiculitis reported in 48 articles indicated a delay between onset of COVID-19 and GBS ranging from 3 to 33 days (39). A total of 42 patients were diagnosed with acute inflammatory demyelinating polyneuropathy, six with acute motor axonal neuropathy, five with Miller-Fisher syndrome, and three with acute motor sensory axonal neuropathy. However, SARS-CoV-2 in the CSF was not detected in any of these patients. Intravenous immunoglobulin was given to 50 patients; eight received plasmapheresis, and two received steroids. Eighteen patients required artificial ventilation, 24 recovered completely, and 23 recovered partially. Two patients died.

The Miller-Fisher variant of GBS, which presents with abnormal muscle coordination, paralysis of the eye muscles, and absence of the tendon reflexes (triad of areflexia, ataxia, and ophthalmoplegia), was also recently reported in another two cases of COVID-19 infection who finally sustained complete neurologic recovery (40).

Apart from olfactory and gustatory dysfunction, now accepted as an early manifestation of COVID-19 infection, isolated oculomotor, trochlear, and facial nerve involvement has also been described (41). Increasing numbers of reports of GBS secondary to COVID-19 are being published. Myalgia is described among the common symptoms of COVID-19, with its duration related to the severity of COVID-19 disease. Few patients with myositis or rhabdomyolysis have been reported as having severe respiratory complications related to COVID-19. A few patients with myasthenia gravis showed exacerbation of their disease after contracting COVID-19; most of these patients recovered with either intravenous immunoglobulins or steroids.

Neuropsychiatric Sequelae of COVID-19

Encephalopathy or delirium. According to a case series of four patients (≥60 years old) of COVID-19-related encephalopathy, patients presented within 0–12 days with various degrees of new-onset cognitive impairment, with predominant frontal lobe impairment: two had cerebellar syndrome, one had myoclonus, one had psychiatric manifestations, and one had status epilepticus (23). No patient had features of encephalitis on MRI or significant CSF abnormalities. Polymerase chain reaction for COVID-19 in the CSF was negative for all patients. All patients presented with a consistent brain fluorodeoxyglucose positron emission tomography CT pattern of abnormalities with frontal hypometabolism and cerebellar hypermetabolism. All patients improved after immunotherapy.

Another case series reported five patients (mean age=66.8 years [SD=7.8]) who developed encephalopathy after a mean of 12.6 days since the onset of COVID-19 symptoms (7). Neurological manifestations included impaired consciousness, agitation, delirium, and pyramidal and extrapyramidal signs; the electroencephalogram showed diffuse slowing in all patients and brain MRI displayed nonspecific findings, while CSF analysis was nonrevealing. Patient recovery was hastened with use of intravenous immunoglobulin (at 0.4 g/kg/day). The authors concluded that intravenous immunoglobulin may represent a safe and effective treatment for COVID-19-associated encephalopathy, with clinical efficacy driven by the anti-inflammatory (anticytokine) action of intravenous immunoglobulin.

In a study of 509 hospitalized COVID-19 patients in whom neurologic manifestations were detected (82.3%) during the course of the disease, encephalopathy (observed in 31.8% of patients) was an independent predictor of worse functional outcome (odds ratio=0.22; $p<0.001$) and higher 30-day mortality (21.7% versus 3.2%; $p<0.001$) (25).

COVID-19 may cause delirium in a significant proportion of patients in the acute stage (8, 42). A case series was recently reported of four patients, each of whom manifested delirium as a result of COVID-19 infection (43). A review of the clinical records of 852 patients admitted for suspected COVID-19 pneumonia indicated that 94 patients (11%) developed delirium during their stay (42). These were older patients (median age=82; $p<0.001$), who had more neuropsychiatric comorbidities and worse respiratory status at baseline. A higher mortality occurred in patients with delirium (57% versus 30%), although this association was not independent of age and respiratory parameters.

In a meta-analysis of 65 peer-reviewed studies assessing acute and chronic sequelae of coronavirus infections, data from patients with COVID-19 were examined that supported a diagnosis of delirium (acute confusional state in 26 out of 40 ICU patients [65%] and agitation in 40 out of 58 ICU patients [69%] in one study and altered consciousness in 17 out of 82 patients [21%] who subsequently died in another study) (8). This meta-analysis also included two reports of hypoxic encephalopathy and one report of encephalitis (8). In a more recent review of 229 studies reporting on prevalence, pathoetiology, or management of delirium in adults with COVID-19, delirium affected >50% of all patients with COVID-19 who were admitted to the ICU (44). The etiology of COVID-19 delirium was deemed multifactorial, with some evidence of direct brain effect.

Neuropsychiatric symptoms and syndromes. CNS infection combined with environmental stress caused by pandemic fear, social and financial restrictions, and ICU monitoring may result in the development of neuropsychiatric symptoms

or syndromes, including depressive symptoms or episodes, manic or hypomanic symptoms or episodes, psychotic symptoms, obsessive-compulsive symptoms, and posttraumatic stress (45). Patients with prior psychiatric disorders may be particularly vulnerable to exacerbations of their psychiatric conditions by COVID-19.

In regard to depression during the COVID-19 pandemic, a meta-analysis of 12 studies showed prevalence rates of depression ranging from 7.45% to 48.30% (46). The pooled prevalence of depression was 25%, with significant heterogeneity between studies ($I^2=99.60\%$, $p<0.001$). The authors concluded that compared with a global estimated prevalence of depression of 3.44% in 2017, a pooled prevalence of 25% appears to be sevenfold higher, thus suggesting an important effect of the COVID-19 outbreak on people's mental health. Similarly, another meta-analysis of 12 studies examining the effect of COVID-19 on mental health and well-being in 27,475 subjects showed that the incidence of depression was 28%; the incidence of anxiety was 25% (47). According to data from two independent longitudinal cohort studies, depression during COVID-19 was similar to prepandemic levels in the young cohort in one study, but those experiencing anxiety almost doubled during COVID-19 (24% versus 13%) (48). In both studies, anxiety and depression during COVID-19 was greater in younger members, in women, in those with pre-existing mental or physical health conditions, and in individuals with adverse socioeconomic status, even when controlling for prepandemic anxiety and depression.

Case reports and case series indicate that COVID-19 infection may increase the risk for psychosis (49, 50). A 52-year-old man with COVID-19 infection with no previous psychiatric history was reported to have developed severe paranoia, which led to a suicide attempt requiring electroconvulsive therapy in addition to antipsychotic drug therapy (49). A 36-year-old woman without prior psychiatric history who was diagnosed with COVID-19 infection was also reported to have developed rapidly progressive change in her behavior, with prominent persecutory delusions and associated insomnia, requiring antipsychotic drug therapy (51). Another case of psychosis was described in a 55-year-old woman with full-blown COVID-19 infection who developed paranoid delusions requiring antipsychotic drug treatment; the psychotic episode lasted for approximately 40 days (52). Another patient, a 41-year-old man, with confirmed COVID-19 infection presented with features consistent with acute mania; he was treated with antipsychotics and anxiolytics (53).

A recent case series of 10 COVID-19 patients was reported where patients presented with psychotic symptoms in the absence of a previous history of psychosis (50). Nine of these cases presented with psychotic symptoms at least 2 weeks after the first symptoms of COVID-19 infection while receiving pharmacological treatment. Structured delusions mixed with features of confusion were the most frequent psychotic symptoms.

A review of 13 studies examining the incidence of psychosis observed during periods of viral epidemics/pandemics (COVID-19, two studies) indicated an increased risk of psychosis in people exposed to a virus during an epidemic or pandemic; 0.9% of people exposed developed psychosis and 4% developed psychotic symptoms (i.e., hallucinations or delusions), contrasting with a median incident rate of 15.2 per 100,000 in the general population (54, 55). One aspect of this problem relates to new cases of psychosis, mostly observed in an older age group, associated with exposure to the psychosocial stress of COVID-19; another aspect relates to a possible virus-induced psychosis (54). Of course, one should keep in mind that COVID-19-related therapy (e.g., steroids) may be responsible for some of the psychiatric problems noted in these patients (see further discussion below) (8).

Even mild COVID-19 disease may confer significant psychological distress and neuropsychiatric symptoms. A study investigated the mental status and inflammatory markers of 103 COVID-19 patients hospitalized with mild symptoms and compared them with those of 103 matched control subjects who were COVID-19 negative. COVID-19 patients, when compared with non-COVID control subjects, manifested higher levels of depression ($p<0.001$), anxiety ($p<0.001$), and posttraumatic stress ($p<0.001$) (56). Female patients showed higher scores compared with male patients and all control subjects. Levels of C-reactive protein correlated positively with the depression score. Qualitative analysis showed similar results regarding negative feelings, such as fear, guilt, and helplessness. Stigma and uncertainty of viral disease progression were two main concerns expressed by COVID-19 patients.

Maladaptive coping styles. The COVID-19 pandemic is a source of persistent and prolonged stress (57). The pandemic has triggered various maladaptive coping styles, including coronaphobia, obsessional cleaning and sanitization, denial or trivialization of symptoms of other illnesses, avoidance of or delayed visits to the emergency room, postponement of scheduled medical procedures, sociophobia, high levels of neuroticism with neurotic reactions at home and at work, lower threshold for quarreling, feelings of frustration, anger, and despair. Health workers have felt strained, burned out, and depressed. Stress, grief, bereavement, mourning and posttraumatic stress have afflicted families who have lost loved ones. Quarantines have had a high psychological impact with negative psychological effects, including posttraumatic stress symptoms, confusion, and anger (58). A review of 13 studies showed increased prevalence of nonpsychotic depression, preanxiety, somatic concerns, alcohol-related disorders, and insomnia in the general population (59). Psychological symptoms correlated more with physical complaints of fatigue and pain in older adults. Frontline workers reported guilt, stigma, anxiety, and poor sleep quality.

LATE NEUROPSYCHIATRIC SEQUELAE

Depression, anxiety, fatigue, posttraumatic stress, and other neuropsychiatric syndromes may become chronic problems

after coronavirus infections. According to a meta-analysis of 65 peer-reviewed studies and seven preprints (94% of studies were of low or medium quality) comprising 3,559 coronavirus cases (mean age ranging from 12.2 years to 68 years) over a follow-up time ranging from 60 days to 12 years, during the acute illness, common symptoms among patients admitted to hospital for SARS or MERS included confusion (27.9%), depression (32.6%), anxiety (35.7%), impaired memory (34.1%), and insomnia (41.9%) (8). Steroid-induced mania and psychosis were reported in 0.7% of patients with SARS in the acute stage in one study. In the post-illness stage, depressed mood (10.5%), insomnia (12.1%), anxiety (12.3%), irritability (12.8%), memory impairment (18.9%), fatigue (19.3%), and (in one study) traumatic memories (30.4%) and sleep disorder (100%) were frequently reported. A recent cross-sectional study examining 18 mostly young patients 20–105 days (median, 85 days) after recovery from mild to moderate COVID-19 disease indicated that 14 (78%) patients reported sustained mild cognitive deficits and performed worse in testing for mild cognitive impairment compared with 10 age-matched healthy control subjects (60).

Neurodegenerative/Neuroimmunological Disorders

A study of 40 patients with mild cognitive impairment (N=20) or mild Alzheimer's disease (N=20) showed a worsening of neuropsychiatric symptoms during 5 weeks of lockdown, with agitation, apathy, and aberrant motor activity being the most common symptoms (61). An interaction between COVID-19 and neurodegenerative disorders (Parkinson's or Alzheimer's disease) as well as neuroimmunological disorders (multiple sclerosis) has also been postulated (62).

Neurodegenerative-disease-related dementias may be risk factors for mortality in COVID-19 patients. COVID-19 may either unmask or trigger neurodegeneration, although these remain unproven theoretical concerns. The hippocampus appears to be particularly vulnerable to COVID-19 infection, however, which may interact with COVID-19-associated cognitive impairment and potentially accelerate symptomatic expression of neurodegenerative disorders, if not neurodegeneration itself (63). Neuropsychiatric symptoms and syndromes produced by SARS-CoV-2 infection and associated psychosocial stressors may worsen the clinical picture and course of these diseases as well.

Similarly, COVID-19 pandemic may exacerbate multiple sclerosis, and patients with multiple sclerosis may be more vulnerable to severe COVID-19 infection, especially older patients and those with previous cardiovascular diseases or with a severe degree of disability (64–66). A recent study of 60 patients with multiple sclerosis and 60 healthy control subjects indicated that the pandemic had a significant impact on the psychological status of patients with multiple sclerosis (67). Compared with the general population, patients with multiple sclerosis presented a higher burden of depressive symptoms and worse sleep quality and perceived an increase in fatigue level.

META-ANALYSES

Several meta-analyses of studies in patients with COVID-19 or other coronaviruses have reported on neuropsychiatric manifestations (Table 1) (8–10, 15, 26, 44, 46, 47, 54, 68–74). A large meta-analysis of 72 studies comprising 3,559 patients with suspected or confirmed SARS coronavirus, MERS coronavirus, or SARS-CoV-2 indicated that during the acute illness, common neuropsychiatric symptoms included confusion, depressed mood, anxiety, impaired memory, and insomnia (8). In the post-illness stage, depression, insomnia, anxiety, irritability, impaired memory, fatigue, traumatic memories, and sleep disorder were frequently reported. When data for patients with COVID-19 were examined, there was evidence for delirium (confusion in 26 [65%] of 40 ICU patients and agitation in 40 [69%] of 58 ICU patients in one study, and altered consciousness in 17 [21%] of 82 patients who subsequently died in another study). At discharge, 15 (33%) of 45 patients with COVID-19 who were assessed had a dysexecutive syndrome in one study. There were also reported two cases of hypoxic encephalopathy and one of encephalitis. As mentioned, a review of 229 studies (77 patient reports, including 37 case reports or series and 40 cohort studies comprising 12,971 patients) indicated that delirium affected >50% of all patients with COVID-19 admitted to the ICU (range 65%−79.5%) (44).

A meta-analysis of 41 studies reporting on neurological manifestations in COVID-19 indicated that the most common specific neurological symptoms were olfactory (35.7%−85.6%) and gustatory (33.3%−88.8%) disorders, especially in mild cases; GBS and acute inflammation of the brain, spinal cord, and meninges were also repeatedly reported after COVID-19 (9).

A meta-analysis of 63 studies specified that the following neurological manifestations were observed in descending order of frequency: olfactory or taste disorders (35.6%), myalgia (18.5%), headache (10.7%), acute cerebral vascular disease (8.1%), dizziness (7.9%), altered mental status (7.8%), seizure (1.5%), encephalitis, neuralgia, ataxia, GBS, Miller-Fisher syndrome, intracerebral hemorrhage, polyneuritis cranialis, and dystonic posture (68). The authors pointed to the cytokine secretion and bloodstream circulation (viremia) as the most possible routes of COVID-19 into the nervous system.

Another meta-analysis of 33 studies with 7,559 participants, mostly from China, indicated that muscle injury or myalgia was the most common (19.2%) neurologic symptom of COVID-19, followed by headache (10.9%), dizziness (8.7%), nausea with or without vomiting (4.6%), concurrent cerebrovascular disease (4.4%), and impaired consciousness (3.8%). Underlying cerebrovascular disease was found in 8.5% of the studies (69).

A meta-analysis of 37 studies (12 retrospective, two prospective, and the rest case reports or series) indicated that the most commonly reported neurological manifestations of COVID-19 were myalgia, headache, altered sensorium, hyposmia, and hypogeusia (70). Uncommonly, COVID-19

TABLE 1. Results of meta-analyses reporting on neuropsychiatric manifestations in COVID-19 patients and individuals without COVID-19 during the pandemic[a]

Study	Number and type of studies	Patients	Outcome	Comments
Rogers et al. (8)	72 (47 studies involved SARS-CoV, 2,068 patients; 13 studies were of MERS-CoV, 515 cases; 12 studies described SARS-CoV-2, 976 patients; 6,390 control subjects) Cohort, cross-sectional, qualitative, case series	3,559 (patients with SARS, MERS, or SARS-CoV-2)	Patients with COVID-19: delirium: confusion in 26 (65%) of 40 ICU patients and agitation in 40 (69%) of 58 ICU patients in one study; altered consciousness in 17 (21%) of 82 patients who subsequently died in another study. At discharge: 15 (33%) of 45 patients had a dysexecutive syndrome in one study. Two reports of hypoxic encephalopathy. One report of encephalitis.	Patients with SARS or MERS had confusion (27.9%), depressed mood (32.6%), anxiety (35.7%), impaired memory (34.1%), insomnia (41.9%), and steroid-induced mania and psychosis (0.7%). In the postillness stage: depression: 35 (10.5%) of 332 patients; insomnia: 34 (12.1%) of 280; anxiety: 21 (12.3%) of 171; irritability: 28 (12.8%) of 218; memory impairment: 44 (18.9%) of 233; traumatic memories: 55 (30.4%) of 181; sleep disorder: 14 (100%) of 14. Point prevalence of PTSD: 32.2% (121 of 402 patients from four studies); depression: 14.9% (77 of 517 patients from five studies); anxiety disorders: 14.8% (42 of 284 patients from three studies).
Wang et al. (9)	41 (20 reporting unspecific neurological symptoms, 20 reporting specific neurological symptoms, and one reporting both; 26 case series, one cohort study, 14 case reports)	4,700 (patients with COVID-19)	Anosmia (35.7%–85.6%) and dysgeusia (33.3%–88.8%), especially in mild cases GBS Acute inflammation of the brain, spinal cord, and meninges repeatedly reported after COVID-19.	Possible underlying mechanisms can include both direct invasion and maladaptive inflammatory responses.
Deng et al. (10)	31 (28 cross-sectional studies, three cohort studies)	5,153 (patients with COVID-19)	Pooled prevalence of depression: 45% (I^2=96%); anxiety: 47% (I^2=97%); and insomnia: 34% (I^2=98%).	No significant differences in the prevalence estimates between genders; however, the depression and anxiety prevalence estimates varied based on different screening tools.
Agyeman et al. (26)	24 (five objective assessments, 19 self-reports)	8,438 (patients with COVID-19)	Pooled proportions of patients presenting with olfactory dysfunction (41%) and gustatory dysfunction (38.2%).	Increasing mean age correlated with lower prevalence of olfactory (coefficient=−0.076; p=0.02) and gustatory (coefficient=−0.073; p=0.03) dysfunctions. There was a higher prevalence of olfactory dysfunctions with the use of objective measurements compared with self-reports (coefficient=2.33; p=0.01). No significant influence of sex.

continued

TABLE 1., *continued*

Study	Number and type of studies	Patients	Outcome	Comments
Hawkins et al. (44)	229 studies/77 patient reports (37 case reports and case series, 40 observational cohort studies)	12,971 (patients with COVID-19)	Delirium affected >50% of all patients with COVID-19 admitted to ICU (range: 65%–79.5%).	Higher rates were reported in those with severe respiratory disease (disorder of consciousness: 38.9% versus 7.2%; OR=8.18; acute confusional syndrome: 14.9% versus 3.9%; OR=4.31; $p<0.001$; confusion: 18.5% versus 0%; $p<0.01$; impaired consciousness: 14.8% versus 2.4%; $p<0.001$). Similarly, studies of older adults found that significant proportions experienced delirium while hospitalized with COVID-19, often associated with age and frailty, ranging from 29% to 40%.
Tsai et al. (68)	50 (11 cohort studies, 11 case series, 28 case reports)	1,326 (patients with COVID-19)	Olfactory/taste disorders: 35.6% Myalgia: 18.5% Headache: 10.7% Acute CVA: 8.1% Dizziness: 7.9% Altered mental status: 7.8% Seizure: 1.5%.	Other manifestations (case reports): encephalitis, neuralgia, ataxia, GBS, Miller-Fisher syndrome, intracerebral hemorrhage, polyneuritis cranialis, and dystonic posture.
Brown et al. (54)	14 (five cross-sectional studies, one survey, one cohort study, one case series, two case reports, three chart reviews, one service evaluation)	14,465 (one cohort chart review: 13,783 psychiatric patients and 35,909 control patients)	0.9%–4% incident cases of psychosis in people infected with COVID-19.	Likely associated with steroid or viral exposure, pre-existing vulnerability, and psychosocial stress.
Bueno-Notivol et al. (46)	12 (online questionnaires)	600–7,236 (non-COVID individuals)	Depression: prevalence rates of 7.45%–48.30%; pooled prevalence of depression was 25%, with significant heterogeneity between studies ($I^2=99.60\%$, $p<0.001$).	Compared with a global estimated prevalence of depression of 3.44% in 2017, a pooled prevalence of 25% is 7 times higher, thus suggesting an important impact of the COVID-19 outbreak on people's mental health.
Ren et al. (47)	12 (cross-sectional studies)	27,475 (21,377 general public/6,098 health care professionals)	Incidence of anxiety (25%; 95% CI=0.19–0.32) and depression (28%; 95% CI=0.17–0.38).	Significant heterogeneity was detected across studies regarding these incidence estimates ($I^2=99.4\%$).
Pinzon et al. (69)	33 (19 cohort studies, 10 retrospective case series or cross-sectional studies, four case reports)	7,559 (patients with COVID-19)	Muscle injury or myalgia was the most common (19.2%) neurologic symptom of COVID-19, followed by headache (10.9%), dizziness (8.7%), nausea with or without vomiting (4.6%), concurrent cerebro-vascular disease (4.4%), and impaired consciousness (3.8%).	Most of the included studies were from China: 29 (88%). Underlying cerebrovascular disease was found in 8.5% of the studies.

continued

TABLE 1., *continued*

Study	Number and type of studies	Patients	Outcome	Comments
Nepal et al. (70)	37 (12 retrospective studies, two prospective studies, 23 case reports/series)	2,647 (patients with COVID-19)	The most commonly reported neurological manifestations of COVID-19 were myalgia (11%–44%), headache (7%–14%), altered sensorium (7%–9%), and hyposmia/hypogeusia (5%–6%).	Uncommonly, COVID-19 can also present with CNS manifestations, such as ischemic stroke, intracerebral hemorrhage, encephalo-myelitis, and acute myelitis; PNS manifestations, such as GBS and Bell's palsy; and skeletal muscle manifestations, such as rhabdomyolysis.
Collantes et al. (71)	49 (one prospective study, 35 retrospective studies, 13 case reports/series)	6,335 (patients with COVID-19)	Proportional point estimates (95% CI): Headache: 0.12 (0.10–0.14; I^2=77%); Dizziness: 0.08; (0.05–0.12; I^2=82%); Headache plus dizziness: 0.09 (0.06–0.13; I^2=0%); Nausea: 0.07 (0.04–0.11; I^2=79%); Vomiting: 0.05 (0.03–0.08; I^2=74%); Nausea plus vomiting: 0.06 (0.03–0.11; I^2=83%); Confusion: 0.05 (0.02–0.14; I^2=86%); and Myalgia: 0.21 (0.18–0.25; I^2=85%).	The most common neurological complication associated with COVID-19 infection was vascular disorders (n=23). Other associated conditions were encephalopathy (n=3), encephalitis (n=1), oculomotor nerve palsy (n=1), isolated sudden-onset anosmia (n=1), GBS (n=1), and Miller-Fisher syndrome (n=2).
Abdullahi et al. (72)	60 (review) 51 (meta-analysis) (46 cohort or cross-sectional studies, four case series, 10 case reports)	11,069 (patients with COVID-19)	Prevalence of neurological/musculoskeletal manifestations was for smell impairment (35%), taste impairment (33%), myalgia (19%), headache (12%), back pain (10%), dizziness (10%), acute cerebrovascular disease (3%), and impaired consciousness (2%).	The majority (58/60) of the studies had excellent methodological quality.
Luo et al. (15)	62	162,639 (COVID and non-COVID individuals)	Pooled prevalence of anxiety (33%) and depression (28%). Prevalence of anxiety (56%) and depression (55%) was the highest among patients with preexisting conditions and COVID-19 infection, and it was similar between health care workers and the general public.	Studies from China, Italy, Turkey, Spain and Iran reported higher pooled prevalence among healthcare workers than the general public. Common risk factors included being a woman or nurse, having lower socioeconomic status, having high risk of contracting COVID-19, and social isolation. Protective factors included having sufficient medical resources and up-to-date and accurate information,

continued

TABLE 1., *continued*

Study	Number and type of studies	Patients	Outcome	Comments
				and taking precautionary measures.
Panda et al. (73)	26 (21 prospective/ retrospective/case series, five case reports)	3,707 (children with COVID-19)	Nonspecific neurological manifestations: headache, myalgia, and fatigue (16.7%). Specific neurological complications: 42 children (1%); encephalopathy (n=25), seizure (n=12), and meningeal signs (n=17).	Rare neurological complications: intracranial hemorrhage, cranial nerve palsy, GBS and vision problems. All children with acute symptomatic seizures survived, suggesting a favorable short-term prognosis.
Panda et al. (74)	15 (cross-sectional studies examining the psychological impact of COVID-19 pandemic)	22,996 (non-COVID children)	Anxiety (34.5%), Depression (41.7%), Irritability (42.3%), and Inattention (30.8%). Behavior/psychological state was affected negatively by the pandemic and quarantine (79.4%). Fear of COVID-19 (22.5%); boredom (35.2%); and sleep disturbance (21.3%).	Caregivers developed anxiety (52.3%) and depression (27.4%), while being in isolation with children.

[a] COVID-19=coronavirus 2019 disease; CVA=cerebrovascular accident; GBS=Guillain-Barré syndrome; ICU=intensive care unit; MERS= Middle East respiratory syndrome coronavirus; OR=odds ratio; PNS=peripheral nervous system; PTSD=posttraumatic stress disorder; SARS-CoV2= severe acute respiratory syndrome coronavirus 2.

presented with CNS manifestations such as ischemic stroke, intracerebral hemorrhage, encephalomyelitis, and acute myelitis; PNS manifestations such as GBS and Bell's palsy; and skeletal muscle manifestations such as rhabdomyolysis.

A meta-analysis of 49 studies involving 6,335 COVID-19 cases showed that the most common neurological complications associated with SARS-CoV-2 infection were vascular disorders (n=23); other associated conditions were encephalopathy (n=3), encephalitis (n=1), oculomotor nerve palsy (n=1), isolated sudden-onset anosmia (n=1), GBS (n=1), and Miller-Fisher syndrome (n=2) (71). Of the neurologically afflicted patients, 14 survived, seven died, and 12 had unclear outcomes.

A meta-analysis of 51 studies (median or mean age ranging from 24 to 95 years) indicated that the prevalence of neurological and musculoskeletal manifestations was 35% for anosmia, 33% for ageusia, 19% for myalgia, 12% for headache, 10% for back pain, 10% for dizziness, 3% for acute cerebrovascular disease, and 2% for impaired consciousness (72).

A meta-analysis of 62 studies (162,639 participants from 17 countries), reporting on the psychological and mental impact of COVID-19 among health care workers, the general population, and patients with higher COVID-19 risk, showed that the pooled prevalence of anxiety and depression was 33% and 28%, respectively (15). The prevalence of anxiety and depression was the highest among patients with pre-existing conditions and SARS-CoV-2 infection (56% and 55%); it was similar between health care workers and the general public. Common risk factors included being a woman, being a nurse, having lower socioeconomic status, having high risk of developing COVID-19, and social isolation. Protective factors included having adequate medical resources, having current and accurate information, and taking precautionary measures.

Finally, a meta-analysis of 21 studies or case series and five case reports in 3,707 pediatric COVID-19 patients indicated that headache, myalgia, and fatigue were predominant nonspecific neurological manifestations, noted in 16.7% of cases (73). A total of 42 children (1%) were reported with definite neurological complications; more complications were reported in those suffering from a severe illness (encephalopathy, 25; seizure, 12; meningeal signs, 17). Rare neurological complications were intracranial hemorrhage, cranial nerve palsy, GBS, and vision problems. All children with acute symptomatic seizures survived, suggesting a favorable short-term prognosis.

NEUROIMAGING

A recent study described the neuroradiological alterations in 167 (4.9%) of 3,404 patients with COVID-19 who presented with neurological signs or symptoms warranting neuroimaging, in whom the most common indications for neuroimaging were delirium (44/167, 26%), focal neurological deficits (37/167, 22%), and altered consciousness (34/167, 20%) (75). Neuroimaging showed abnormalities in 23% of patients, with use of MRI in 20 patients and CT in 18 patients. The most consistent neuroradiological finding was microhemorrhage with a

predilection for the splenium of the corpus callosum (12/20, 60%), followed by acute or subacute infarct (5/20, 25%), watershed white matter hyperintensities (4/20, 20%) and susceptibility changes on susceptibility-weighted imaging in the superficial veins (3/20, 15%), acute hemorrhagic necrotizing encephalopathy (2/20, 10%), large parenchymal hemorrhage (2/20, 10%), subarachnoid hemorrhage (1/20, 5%), hypoxic-ischemic changes (1/20, 5%), and acute disseminated encephalomyelitis-like changes (1/20, 5%). The authors suggested that prolonged hypoxemia, consumption coagulopathy, and endothelial disruption may be the likely underlying pathological mechanisms reflecting disease severity in this particular group.

NEUROPSYCHIATRIC ADVERSE EFFECTS OF COVID-19 TREATMENT

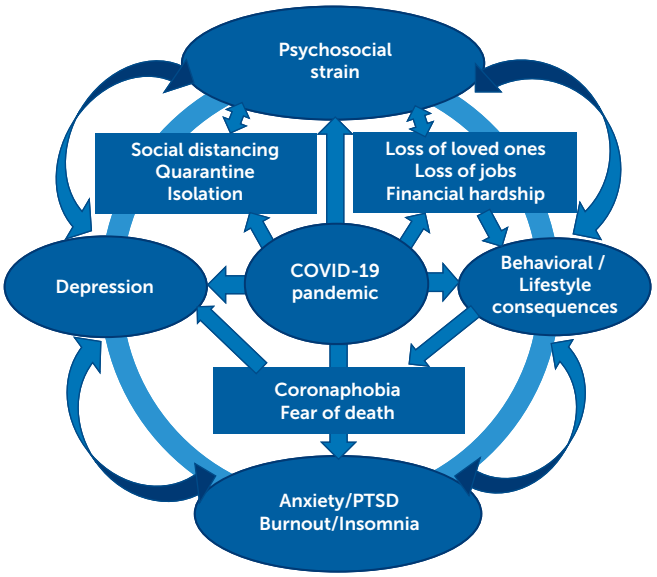
According to a study investigating adverse events with the use of chloroquine (or hydroxychloroquine) reported to the U.S. Food and Drug Administration Adverse Event Reporting System database between 2012 and 2019, 520 cases (12%) with neuropsychiatric adverse effects were reported among 4,336 case reports with exposure to chloroquine (76). Specifically, exposure to chloroquine was associated with a significant high reporting of amnesia, delirium, hallucinations, depression, and loss of consciousness. There was no significant high reporting of suicide, psychosis, confusion, and agitation. Importantly, current pharmacovigilance study results did not suggest any potential link between the use of chloroquine and an increased risk of suicide, psychosis, confusion, and agitation, which would be informative during the emergency use of chloroquine for the treatment of COVID-19.

According to a large meta-analysis reporting on neuropsychiatric presentations associated with severe coronavirus infections, steroid-induced mania and psychosis were reported in 13 (0.7%) of 1,744 patients with SARS in the acute stage in one study (8).

HEALTH CARE WORKERS

The COVID-19 pandemic has had apparent psychiatric repercussions in health care workers (14). According to a review of seven articles (N=7,741), the anxiety level of medical workers has increased significantly during the epidemic of COVID-19 (77). Another recent study from China found that physicians also experienced an increase in mental health symptoms, with fear of violence and a decline in mood, after the COVID-19 outbreak (78). In particular, among 385 physicians in training (247 women; median age 25 years), for the 2019 to 2020 cohort, daily mood scores decreased significantly between quarter 1 and quarter 2 ($\beta = -0.50$; $P=0.002$; β refers to the change between quarters 1 and 2) compared with quarter 1 and quarter 2 for the 2018 to 2019 cohort. Also, scores for symptoms of depression ($\beta=0.61$; $P=0.02$) and anxiety ($\beta=0.64$; $P=0.008$) increased significantly during this period. In addition, fear of violence (odds ratio, 2.36; $P<0.001$) and

FIGURE 2. Spectrum of neuropsychiatric manifestations that develop in noninfected patients and individuals during the COVID-19 pandemic[a]



[a] Data shown are for health care workers, as well as individuals in the general public. PTSD=posttraumatic stress disorder.

observation of violence from patients or their families (odds ratio, 3.63, $P<0.001$) increased significantly (78). Even an episode of brief reactive psychosis has been reported in a general practitioner under stressful circumstances derived from COVID-19 (79).

A cross-sectional study of 502 health care providers during the pandemic indicated that 55% had depressive disorder, which ranged from mild (24.9%) to moderate (14.5%) and moderately severe (10%) to severe (5.8%) (80). More than 50% had generalized anxiety disorder, which ranged from mild (25.1%) and moderate (11%) to severe (15.3%). Multivariate analysis showed that males were significantly less likely to have anxiety; the 30–39 years age group was significantly more likely to have depression and anxiety; and nurses had a significantly higher mean score of anxiety.

A systematic review of 15 studies comparing the incidence of psychological issues during the COVID-19 pandemic in health care workers and non-health care workers indicated that even though reasons for psychological distress in these two groups may be different, both suffered from psychological issues (anxiety, depression, occupational stress, posttraumatic stress, and insomnia) in equal measures—except for insomnia, which was reported at a significantly higher incidence among health care workers (81).

A meta-analysis of 13 studies (33,062 participants) reporting on the mental health of health care workers showed that anxiety (assessed in 12 studies) had a pooled prevalence of 23.2%, while depression (10 studies) had a prevalence rate of 22.8% (82). Female health care workers and nurses exhibited higher rates of affective symptoms compared with

male health care workers and medical staff, respectively. Insomnia prevalence was estimated at 38.9% across five studies.

Finally, a meta-analysis of 117 studies examining the impact of viral epidemic outbreaks on health care workers' mental health found that the pooled prevalence was higher for acute stress disorder (40%), followed by anxiety (30%), burnout (28%), depression (24%), and posttraumatic stress (13%) (83).

PSYCHOSOCIAL IMPACT

Public health instructions and governmental measures to confine spreading of COVID-19 during the pandemic have imposed restrictions on daily living such as social distancing, quarantine, isolation, and home confinement and have had a serious impact on psychosocial health (84). Additionally, loss of life, lost or decreased job availability, fear of contracting the virus, travel restrictions, and consequent financial hardship have ushered in a new inimical reality and life situation.

Thus, the pandemic has created an unprecedented socioeconomic tumult that has led to anxiety, coronaphobia, obsessive behavior, paranoia, depression, and posttraumatic stress (2) (Figure 2). A meta-analysis of studies examining the impact of COVID-19 pandemic on public mental health showed a prevalence of stress in five studies with a total sample size of 9,074 at 29.6%, the prevalence of anxiety in 17 studies with a sample size of 63,439 at 31.9%, and the prevalence of depression in 14 studies with a sample size of 44,531 people at 33.7% (85). A recent review of eight studies reporting mental health outcomes of quarantine or isolation in any population (most of the primary studies were conducted in high-income nations and in hospital settings) indicated a high burden of mental health problems among patients, informal caregivers, and health care providers who experienced quarantine or isolation (86). Prevalent mental health problems included depression, anxiety, mood disorders, psychological distress, posttraumatic stress, insomnia, fear, stigmatization, low self-esteem, and lack of self-control.

A meta-analysis of 15 studies comprising 22,996 children and adolescents indicated that during the COVID-19 pandemic, children often suffered from anxiety (34.5%), depression (41.7%), irritability (42.3%), and inattention (30.8%) (74). The behavior or psychological state of 79.4% of children was affected negatively by the pandemic and quarantine; at least 22.5% of children had a significant fear of COVID-19, 35.2% had boredom, and 21.3% had sleep disturbance. In the same line, 52.3% and 27.4% of caregivers developed anxiety and depression, respectively, while in isolation with children.

CONCLUSIONS

Evidence is accumulating that SARS-CoV-2 can penetrate the CNS through the olfactory or circulatory route and thus produce a direct effect on the CNS and PNS of infected patients, with manifestations that include anosmia and dysgeusia, encephalopathy, stroke, epilepsy, GBS, and other neuromuscular disorders, as well as an indirect influence on brain functions by causing cytokine storm and inducing delayed immune-mediated processes. Furthermore, the virus has been implicated in maladaptive coping styles and major neuropsychiatric symptoms and syndromes, including anxiety, depression, delirium, and paranoia. The COVID-19 pandemic has further created an unprecedented socioeconomic turmoil that has led to severe psychosocial impact with widespread stress, anxiety, and depressed mood, triggering or exacerbating mental health in noninfected individuals in the society at large.

There is an immediate need for interventions aimed at managing the psychosocial impact and mitigate the neuropsychiatric manifestations in addition to the other health and economic consequences of this unprecedented viral pandemic. Protection of mental well-being can be accomplished by providing programs structured for psychosocial support to all those in need, such as health care workers, persons stricken by unemployment and financial hardship, families with COVID-19-affected members, older adults, and other vulnerable groups.

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REFERENCES

1. Manolis AS, Manolis TA: Cardiovascular complications of the coronavirus (COVID-19) infection. Rhythmos 2020; 15:23–28
2. Dubey S, Biswas P, Ghosh R, et al: Psychosocial impact of COVID-19. Diabetes Metab Syndr 2020; 14:779–788
3. Ceylan RF, Ozkan B, Mulazimogullari E: Historical evidence for economic effects of COVID-19. Eur J Health Econ 2020; 21:817–823
4. Roy D, Ghosh R, Dubey S, et al: Neurological and neuropsychiatric impacts of COVID-19 pandemic. Can J Neurol Sci 2021; 48:9–24
5. Szcześniak D, Gładka A, Misiak B, et al: The SARS-CoV-2 and mental health: from biological mechanisms to social consequences. Prog Neuropsychopharmacol Biol Psychiatry 2021; 104:110046
6. Muccioli L, Pensato U, Cani I, et al: COVID-19-related encephalopathy presenting with aphasia resolving following tocilizumab treatment. J Neuroimmunol 2020; 349:577400
7. Muccioli L, Pensato U, Bernabè G, et al: Intravenous immunoglobulin therapy in COVID-19-related encephalopathy. J Neurol (Epub ahead of print, October 8, 2020)
8. Rogers JP, Chesney E, Oliver D, et al: Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7:611–627

9. Wang L, Shen Y, Li M, et al: Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. J Neurol 2020; 267:2777–2789
10. Deng J, Zhou F, Hou W, et al.: The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci 2020; 1486:90–111
11. Varatharaj A, Thomas N, Ellul MA, et al: Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020; 7:875–882
12. Henssler J, Stock F, van Bohemen J, et al: Mental health effects of infection containment strategies: quarantine and isolation-a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2020; 271:223–234
13. Krishnamoorthy Y, Nagarajan R, Saya GK, et al: Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: a systematic review and meta-analysis. Psychiatry Res 2020; 293: 113382
14. da Silva FCT, Neto MLR: Psychiatric symptomatology associated with depression, anxiety, distress, and insomnia in health professionals working in patients affected by COVID-19: a systematic review with meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2021; 104:110057
15. Luo M, Guo L, Yu M, et al: The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public: a systematic review and meta-analysis. Psychiatry Res 2020; 291:113190
16. Puccioni-Sohler M, Poton AR, Franklin M, et al: Current evidence of neurological features, diagnosis, and neuropathogenesis associated with COVID-19. Rev Soc Bras Med Trop 2020; 53:e20200477
17. Wenting A, Gruters A, van Os Y, et al: COVID-19 neurological manifestations and underlying mechanisms: a scoping review. Front Psychiatry 2020; 11:860
18. Correia AO, Feitosa PWG, Moreira JLS, et al: Neurological manifestations of COVID-19 and other coronaviruses: a systematic review. Neurol Psychiatry Brain Res 2020; 37:27–32
19. Koralnik IJ, Tyler KL: COVID-19: a global threat to the nervous system. Ann Neurol 2020; 88:1–11
20. Guilmot A, Maldonado Slootjes S, Sellimi A, et al: Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. J Neurol 2020; 268:751–757
21. Ghosh R, Dubey S, Finsterer J, et al: SARS-CoV-2-associated acute hemorrhagic, necrotizing encephalitis (AHNE) presenting with cognitive impairment in a 44-year-old woman without comorbidities: a case report. Am J Case Rep 2020; 21:e925641
22. Díaz-Pérez C, Ramos C, López-Cruz A, et al: Acutely altered mental status as the main clinical presentation of multiple strokes in critically ill patients with COVID-19. Neurol Sci 2020; 41:2681–2684
23. Delorme C, Paccoud O, Kas A, et al: Covid-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. Eur J Neurol 2020; 27:2651–2657
24. Rifino N, Censori B, Agazzi E, et al: Neurologic manifestations in 1760 COVID-19 patients admitted to Papa Giovanni XXIII Hospital, Bergamo, Italy. J Neurol 2021; 268:2331–2338
25. Liotta EM, Batra A, Clark JR, et al: Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. Ann Clin Transl Neurol 2020; 7:2221–2230
26. Agyeman AA, Chin KL, Landersdorfer CB, et al: Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. Mayo Clin Proc 2020; 95:1621–1631
27. Yazdanpanah N, Saghazadeh A, Rezaei N: Anosmia: a missing link in the neuroimmunology of coronavirus disease 2019 (COVID-19). Rev Neurosci 2020; 31:691–701
28. Xiong W, Mu J, Guo J, et al: New onset neurologic events in people with COVID-19 in 3 regions in China. Neurology 2020; 95:e1479–e1487
29. Tiwari A, Berekashvili K, Vulkanov V, et al: Etiologic subtypes of ischemic stroke in SARS-CoV-2 patients in a cohort of New York City hospitals. Front Neurol 2020; 11:1004
30. Sweid A, Hammoud B, Bekelis K, et al: Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke 2020; 15:733–742
31. Shahjouei S, Naderi S, Li J, et al: Risk of stroke in hospitalized SARS-CoV-2 infected patients: a multinational study. EBioMedicine 2020; 59:102939
32. Sun M, Ruan X, Li Y, et al. Clinical characteristics of 30 COVID-19 patients with epilepsy: a retrospective study in Wuhan. Int J Infect Dis 2020; 103:647–653
33. Vohora D, Jain S, Tripathi M, et al: COVID-19 and seizures: is there a link? Epilepsia 2020; 61:1840–1853
34. Nikbakht F, Mohammadkhanizadeh A, Mohammadi E: How does the COVID-19 cause seizure and epilepsy in patients? the potential mechanisms. Mult Scler Relat Disord 2020; 46:102535
35. Lu L, Xiong W, Liu D, et al: New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. Epilepsia 2020; 61:e49–e53
36. Katyal N, Narula N, Acharya S, et al: Neuromuscular complications with SARS-COV-2 infection: a review. Front Neurol 2020; 11:1052
37. Uncini A, Vallat JM, Jacobs BC: Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry 2020; 91: 1105–1110
38. De Sanctis P, Doneddu PE, Viganò L, et al: Guillain-Barré syndrome associated with SARS-CoV-2 infection: a systematic review. Eur J Neurol 2020; 27:2361–2370
39. Finsterer J, Scorza FA, Fiorini AC: SARS-CoV-2-associated Guillain-Barre syndrome in 62 patients. Eur J Neurol 2021; 28: e10–e12
40. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al: Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology 2020; 95:e601–e605
41. Paliwal VK, Garg RK, Gupta A, et al: Neuromuscular presentations in patients with COVID-19. Neurol Sci 2020; 41:3039–3056
42. Ticinesi A, Cerundolo N, Parise A, et al: Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. Aging Clin Exp Res 2020; 32: 2159–2166
43. Beach SR, Praschan NC, Hogan C, et al: Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen Hosp Psychiatry 2020; 65:47–53
44. Hawkins M, Sockalingam S, Bonato S, et al: A rapid review of the pathoetiology, presentation, and management of delirium in adults with COVID-19. J Psychosom Res 2021; 141:Article 110350
45. Steardo L Jr, Steardo L, Verkhratsky A: Psychiatric face of COVID-19. Transl Psychiatry 2020; 10:261
46. Bueno-Notivol J, Gracia-García P, Olaya B, et al: Prevalence of depression during the COVID-19 outbreak: a meta-analysis of community-based studies. Int J Clin Health Psychol 2021; 21: 100196
47. Ren X, Huang W, Pan H, et al: Mental health during the Covid-19 outbreak in China: a meta-analysis. Psychiatr Q 2020; 91:1033–1045
48. Kwong ASF, Pearson RM, Adams MJ, et al: Mental health before and during the COVID-19 pandemic in two longitudinal UK population cohorts. Br J Psychiatry (Epub ahead of print, November 24, 2020)
49. Chacko M, Job A, Caston F 3rd, et al: COVID-19-induced psychosis and suicidal behavior: case report. SN Compr Clin Med (Epub ahead of print, September 26, 2020)

50. Parra A, Juanes A, Losada CP, et al: Psychotic symptoms in COVID-19 patients: a retrospective descriptive study. Psychiatry Res 2020; 291:113254
51. Smith CM, Komisar JR, Mourad A, et al: COVID-19-associated brief psychotic disorder. BMJ Case Rep 2020; 13:e236940
52. Lim ST, Janaway B, Costello H, et al: Persistent psychotic symptoms following COVID-19 infection. BJPsych Open 2020; 6:e105
53. Mawhinney JA, Wilcock C, Haboubi H, et al: Neurotropism of SARS-CoV-2: COVID-19 presenting with an acute manic episode. BMJ Case Rep 2020; 13:e236123
54. Brown E, Gray R, Lo Monaco S, et al: The potential impact of COVID-19 on psychosis: a rapid review of contemporary epidemic and pandemic research. Schizophr Res 2020; 222:79–87
55. McGrath J, Saha S, Welham J, et al: A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004; 2:13
56. Guo Q, Zheng Y, Shi J, et al: Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun 2020; 88:17–27
57. Blackman JS: A psychoanalytic view of reactions to the coronavirus pandemic in China. Am J Psychoanal 2020; 80:119–132
58. Brooks SK, Webster RK, Smith LE, et al: The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395:912–920
59. Banerjee D, Vaishnav M, Rao TS, et al: Impact of the COVID-19 pandemic on psychosocial health and well-being in South-Asian (World Psychiatric Association zone 16) countries: a systematic and advocacy review from the Indian Psychiatric Society. Indian J Psychiatry 2020; 62(Suppl 3):S343–S353
60. Woo MS, Malsy J, Pöttgen J, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. Brain Commun 2020; 2: fcaa205
61. Lara B, Carnes A, Dakterzada F, et al: Neuropsychiatric symptoms and quality of life in Spanish patients with Alzheimer's disease during the COVID-19 lockdown. Eur J Neurol 2020; 27:1744–1747
62. Ferini-Strambi L, Salsone M: COVID-19 and neurological disorders: are neurodegenerative or neuroimmunological diseases more vulnerable? J Neurol 2020; 268:409–419
63. Ritchie K, Chan D, Watermeyer T. The cognitive consequences of the COVID-19 epidemic: collateral damage? Brain Commun 2020; 2:fcaa069
64. Zabalza A, Cárdenas-Robledo S, Tagliani P, et al: COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur J Neurol (Epub ahead of print, December 19, 2020)
65. Chaudhry F, Bulka H, Rathnam AS, et al: COVID-19 in multiple sclerosis patients and risk factors for severe infection. J Neurol Sci 2020; 418:117147
66. Möhn N, Konen FF, Pul R, et al: Experience in multiple sclerosis patients with COVID-19 and disease-modifying therapies: a review of 873 published cases. J Clin Med 2020; 9:4067
67. Motolese F, Rossi M, Albergo G, et al: The psychological impact of COVID-19 pandemic on people with multiple sclerosis. Front Neurol 2020; 11:580507
68. Tsai ST, Lu MK, San S, et al: The neurologic manifestations of coronavirus disease 2019 pandemic: a systemic review. Front Neurol 2020; 11:498
69. Pinzon RT, Wijaya VO, Buana RB, et al: Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Front Neurol 2020; 11:565
70. Nepal G, Rehrig JH, Shrestha GS, et al: Neurological manifestations of COVID-19: a systematic review. Crit Care 2020; 24:421
71. Collantes MEV, Espiritu AI, Sy MCC, et al: Neurological manifestations in COVID-19 infection: a systematic review and meta-analysis. Can J Neurol Sci 2020; 48:66–76
72. Abdullahi A, Candan SA, Abba MA, et al: Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front Neurol 2020; 11:687
73. Panda PK, Sharawat IK, Panda P, et al: Neurological complications of SARS-CoV-2 infection in children: a systematic review and meta-analysis. J Trop Pediatr (Epub ahead of print, September 10, 2020)
74. Panda PK, Gupta J, Chowdhury SR, et al: Psychological and behavioral impact of lockdown and quarantine measures for COVID-19 pandemic on children, adolescents and caregivers: a systematic review and meta-analysis. J Trop Pediatr 2021; 67:fmaa122
75. Sawlani V, Scotton S, Nader K, et al: COVID-19-related intracranial imaging findings: a large single-centre experience. Clin Radiol 2021; 76:108–116
76. Sato K, Mano T, Iwata A, et al: Neuropsychiatric adverse events of chloroquine: a real-world pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database. Biosci Trends 2020; 14:139–143
77. Pan R, Zhang L, Pan J: The anxiety status of Chinese medical workers during the epidemic of COVID-19: a meta-analysis. Psychiatry Investig 2020; 17:475–480
78. Li W, Frank E, Zhao Z, et al: Mental health of young physicians in China during the novel coronavirus disease 2019 outbreak. JAMA Netw Open 2020; 3:e2010705
79. Anmella G, Fico G, Roca A, et al: Unravelling potential severe psychiatric repercussions on healthcare professionals during the COVID-19 crisis. J Affect Disord 2020; 273:422–424
80. AlAteeq DA, Aljhani S, Althiyabi I, et al: Mental health among healthcare providers during coronavirus disease (COVID-19) outbreak in Saudi Arabia. J Infect Public Health 2020; 13: 1432–1437
81. Sheraton M, Deo N, Dutt T, et al: Psychological effects of the COVID 19 pandemic on healthcare workers globally: a systematic review. Psychiatry Res 2020; 292:113360
82. Pappa S, Ntella V, Giannakas T, et al: Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Brain Behav Immun 2020; 88:901–907
83. Serrano-Ripoll MJ, Meneses-Echavez JF, Ricci-Cabello I, et al: Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review and meta-analysis. J Affect Disord 2020; 277:347–357
84. Ammar A, Chtourou H, Boukhris O, et al: COVID-19 home confinement negatively impacts social participation and life satisfaction: a worldwide multicenter study. Int J Environ Res Public Health 2020; 17:6237
85. Salari N, Hosseinian-Far A, Jalali R, et al: Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Global Health 2020; 16:57
86. Hossain MM, Sultana A, Purohit N: Mental health outcomes of quarantine and isolation for infection prevention: a systematic umbrella review of the global evidence. Epidemiol Health 2020; 42:e2020038