APA Resource Document

Resource Document on Acute Neuropsychiatric Sequelae of COVID-19 Infection

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Authors: Scott Beach, Nadia Cacodcar, Erica Baller, Jon Levenson

Introduction

This resource document will describe acute neuropsychiatric sequelae of COVID-19 infection. Importantly, the literature on neuropsychiatric manifestations of COVID-19 continues to evolve rapidly, and many of the largest and best studies were based on early waves and variants. Very little data exist on neuropsychiatric sequelae of infection with micron subvariants, suggesting that some data may not be generalizable to the current pandemic state. "This paper will synthesize and summarize the current state of knowledge about neuropsychiatric sequelae in the context of COVID-19. It will need to be updated as more literature emerges."

Acute Neuropsychiatric Sequelae of COVID-19

Reports of acute neuropsychiatric sequelae of COVID-19 emerged almost immediately after the virus was recognized. Early studies estimated that 22.5% of patients will develop neuropsychiatric symptoms during an acute infection by SARS-CoV-2 (Nalleballe et al., 2020). In the first wave of the pandemic, nearly 50% of affected patients reported anosmia or ageusia, suggesting that the virus was impacting sensory systems and might have neuroinvasive potential (Butowt et al., 2020). Other neurological illnesses have also been associated with COVID-19, including cerebrovascular accidents (CVA), encephalitis, posterior reversible encephalopathy syndrome, dysautonomia, tinnitus, and seizures (Varatharaj et al., 2020). With newer variants, rates appear to be decreasing. However, 10%–20% of infections with omicron variants are still associated with anosmia or ageusia (Butowt et al., 2022). With regard to acute psychiatric manifestations of COVID-19, the three most commonly described phenomena, which will serve as the focus of this section of the resource document, are delirium, nondeliria psychoses, and catatonia and related syndromes.

Among patients with neuropsychiatric manifestations of COVID-19, workup is often unrevealing or nonspecific. Large case series have suggested that an electroencephalogram (EEG) usually shows nonspecific diffuse background slowing, indicative of delirium/encephalopathy (Helms et al., 2020). Few patients have evidence of seizure activity on an EEG, though risk for epilepsy is increased for patients

who have preexisting neurological risk factors for seizures (Taquet et al., 2023). Similarly, in patients who undergo lumbar puncture, cerebrospinal fluid (CSF) findings are generally nonspecific. Some patients have demonstrated elevated protein and oligoclonal bands, both associated with inflammation, but only a minority (less than 6% in one study of patients with neuropsychiatric manifestations who had CSF tested) have virus isolated in CSF (Helms et al., 2020). Magnetic resonance imaging (MRI) is normal in most patients with neuropsychiatric findings. However, several specific patterns have been described in a minority of patients, with the most common involving signal abnormalities in the medial temporal lobes, similar to what is sometimes seen with anti-NMDA-receptor-antibody encephalitis (Helms et al., 2020). Other patterns involve lesions indicative of diffuse microhemorrhages. In a small series of patients with acute neuropsychiatric sequelae of COVID-19 infection, magnetic resonance spectroscopy demonstrated a pattern similar to that seen with delayed post-hypoxic leukoencephalopathy in some patients (Nersesjan et al., 2022). Finally, autopsy studies have provided conflicting evidence, with most (but not all) studies failing to identify SARS-CoV-2 RNA in brain tissue (Satturwar et al., 2021; Matschke et al., 2020). This may reflect the length of time between infection and autopsy, with longer gaps associated with a decreased likelihood of identifying RNA in brain tissue (Maccio et al., 2022).

Delirium

As emergency departments and hospitals began to fill with COVID-19-positive patients in the first COVID-19 wave in the spring of 2020, neuropsychiatric manifestations were increasingly recognized, with delirium affecting a significant portion of those infected. COVID-19 delirium can present in a variety of ways but is typically characterized by a sudden change in mentation in the setting of infection. For many patients with delirium in the setting of COVID-19, altered mental status is associated with severe respiratory illness, such as pneumonia and acute respiratory distress syndrome (ARDS). Between 73% and 83% of patients in intensive care units (ICU) will develop delirium (Beckwith et al., 2023; Khan et al., 2020). Conversely, delirium has also been described in otherwise asymptomatic patients, with one study suggesting that altered mental status was the 6th most common presenting feature of acute COVID-19 infection and that nearly one-third of patients presenting with delirium and found to be COVID-19-positive did not have other physical signs (Kennedy et al., 2020).

Many COVID-19-positive patients presented with classic features of delirium, including inattention, cognitive dysfunction, perceptual disturbances, and agitation, and exhibited a waxing and waning course. However, delirium in the setting of COVID-19 has also been associated with atypical motor and amotivational symptoms, including myoclonus, rigidity, withdrawal (decreased eating and drinking), alogia, and abulia (Beckwith et al., 2023). These features suggest the possible involvement of the dopaminergic system, which drives movement and behavior (discussed further in the Catatonia and Related Syndromes section). Studies have been mixed with regard to motoric subtype, with some finding hyperactive features to be more common while another prominent study found a substantial majority of hypoactive patients (Khan et al., 2020). Mortality in COVID-19 delirium has been linked to higher frequency of pulmonary infections, mechanical ventilation, and vasopressor use as well as longer admissions. Laboratory and CSF findings showing elevated inflammatory markers have been reported in numerous studies (C-reactive protein (CRP), D-dimer, lactate dehydrogenase) (García-Grimshaw et al., 2022; Edén et al., 2022). García-Grimshaw et al. notably looked at neutrophil-to-lymphocyte ratios (NLRs) upon admission and found that an NLR ≥ 9, indicating high physiologic stress, was strongly associated with in-hospital delirium (García-Grimshaw et al., 2022).

The unique clinical features of COVID-19 delirium suggest distinct pathophysiologic mechanisms that link COVID-19 infection with altered mental status. One avenue of research has focused on direct invasion of the virus into the brain. Early work into previous SARS (severe acute respiratory syndrome) demonstrated that it has neuroinvasive potential. One animal study found SARS-CoV-1 RNA in the hypothalamus and brainstem of those infected, while another looking at MERS (Middle East respiratory syndrome) also showed MRI abnormalities with hyperintensities noted in the cortex, basal ganglia, brainstem, and cerebellum (Gu et al., 2005; Saad et al., 2014). In an autopsy study by Meinhardt et al., two-thirds of those infected had the virus in their nasal mucosa and one-third had it in the olfactory bulb and cerebellum (Meinhardt et al., 2021), suggesting neuroinvasive potential existed for SARS-CoV-2 as well. Direct invasion is further supported in that brain regions found to be afflicted by the virus correlate with the motoric abnormalities being found on exams in COVID-19 patients. However, there has been controversy. In a study by Llorens et al., results show substantial reductions in viral concentration inside the brain (Llorens et al., 2021). While a small number of patients had evidence of central nervous system (CNS) invasion, many more without such evidence still presented with delirium during infection, suggesting that other pathophysiologic mechanisms may be contributing to altered mental status. Researchers have suggested that COVID-19 causes altered mentation by mechanisms such as inflammation, molecular mimicry, and hematogenous spread (Cappello et al., 2020; Thakur et al., 2021; Teuwen et al., 2020).

One hypothesis linking COVID-19 infection to altered mental status is via disruption of the blood-brain barrier. Direct infection of endothelial cells via ACE2 receptor binding and the proinflammatory state triggered by SARS-CoV-2 contribute to blood-brain barrier dysfunction (García-Grimshaw et al., 2022). The orbitofrontal cortex is particularly vulnerable to blood-brain barrier disruption, making it more susceptible to direct and indirect invasion with infected macrophages crossing through the epithelium. The orbitofrontal region also notably contains dopaminergic projections, the deterioration of which would clinically correlate with motoric symptoms such as abulia, immobility, and withdrawal. Such cellular senescence has been identified by Chen et al. (Chen et al., 2021).

Newer hypotheses propose that the SARS-CoV-2 virus targets alveolar endothelial cells, triggering blood clotting (hemostasis?) and inflammation as well as leakage of contents into neighboring capillaries (Teuwen et al., 2020). Such hematogenous spread could also occur through the mucus clearance system, allowing entry to the gastrointestinal system, where the virus is then absorbed through the gut and into the bloodstream. There have also been cases that suggest molecular mimicry and autoimmunity as other potential mechanisms (Cappello et al., 2020). Taken together, these data suggest that there is substantial heterogeneity in the trigger for delirium in those with COVID-19 and that individual risk factors and clinical presentation should be considered in evaluation and management.

The most common risk factor for delirium associated with COVID-19 is age. Among elderly patients who were hospitalized with COVID-19, 34% developed delirium, as did 83% of COVID-19 patients being managed in ICUs (Beckwith et al., 2023). In the general population, as with other non-COVID-19 delirium, disruptive environment, restraint use, illness severity, age, preexisting neurocognitive disease, use of mechanical ventilation, and increased use of deliriogenic sedative agents have been associated with COVID-19 delirium. However, other risk factors specific to COVID-19 delirium have now been identified. One international cohort study showed that delirium was more common and more prolonged in patients with severe COVID-19 infections compared to those with non-COVID-19 acute respiratory failure (Pun et al., 2021). Researchers have also investigated the unique impact of

quarantine, noting reduced risk of delirium with family visitation, which was abolished early during the COVID-19 outbreak (Pun et al., 2021). As hospitals adjusted to the demands of the pandemic, some of the changes needed for infection control were also in conflict with the tenets of delirium prevention, thus increasing risk for delirium (Inouye, 2021). Interventions like early mobilization, frequent orientation, and clear communication are staples in delirium prevention and treatment (Fong, 2022). However, during the pandemic, patients were confined to their rooms, interactions were often kept brief to minimize staff exposure, and the communication that did take place in person was muffled through masks.

As with delirium not associated with COVID-19, COVID-19 delirium should be managed with both nonpharmacologic and pharmacologic approaches. First, management begins by optimizing behavioral interventions to avoid or minimize the use of CNS medications and restraints. Over the past three years, implementation of behavioral techniques has improved. However, some practices like reorientation and redirection, which require the consistent presence of family or sitters, may be limited in the setting of COVID-19 depending on hospital quarantine, isolation, and visitation restrictions. Ready access to tablets and phones, early mobilization, and consolidation of nighttime disruptions have been successfully utilized in treatment. For ICU patients, the ABCDEF bundle (Assess, prevent, and manage pain; Both spontaneous awakening trials and spontaneous breathing trials; Choice of analgesia and sedation; Delirium: assess, prevent, and manage; Early mobility and exercise; and Family engagement and empowerment) has been demonstrated to reduce rates of delirium, though not specifically in COVID-19 patients.

Similarly, few studies have evaluated nonpharmacologic treatments for COVID-19 delirium specifically. For example, in common delirium management practice for those on mechanical ventilation, teams often consider light sedation, minimal use of neuromuscular blockade, and frequent awakening and breathing trials (Pun et al., 2021; Girard et al., 2008). However, during the first wave of COVID-19, the ARDS was so profound that patients required deep sedation, high positive end-expiratory pressures, and proning to maintain oxygenation (Flinspach et al., 2021; Mittermaier et al., 2020). In contrast, omicron variants are less associated with lower respiratory tract infection, and previous delirium prevention recommendations might be appropriate (Piersiala et al., 2022; Kozlov, 2022). Choice of sedative agents for ICU patients is also critical, with non-COVID-19 studies demonstrating lower rates of delirium in patients treated with dexmedetomidine compared to older agents such as fentanyl and midazolam (Riker et al., 2009). In COVID-19 delirium, the authors have also seen benefits with dexmedetomidine (Baller et al., 2020). In cases where patients are experiencing perceptual disturbances or significant agitation that interfere with the safety of the patient or clinical team, the addition of pharmacologic treatment should be considered.

Though treatment plans will vary case by case, there are unique management considerations for patients with COVID-19 delirium. Given reports of increased tone and akinetic mutism, low-potency atypical antipsychotics that block the dopamine D2 receptor and muscarinic receptors may be favorable for treating psychosis while avoiding extrapyramidal symptoms (EPS) (Beckwith et al., 2023). However, these medications may also worsen delirium due to anticholinergic burden. Another consideration is the selection of agents that spare the respiratory centers given the risk of respiratory failure in patients with COVID-19 pneumonia. Additionally, SARS-CoV-2 can deposit in the heart tissue and may increase the risk for QTc prolongation.

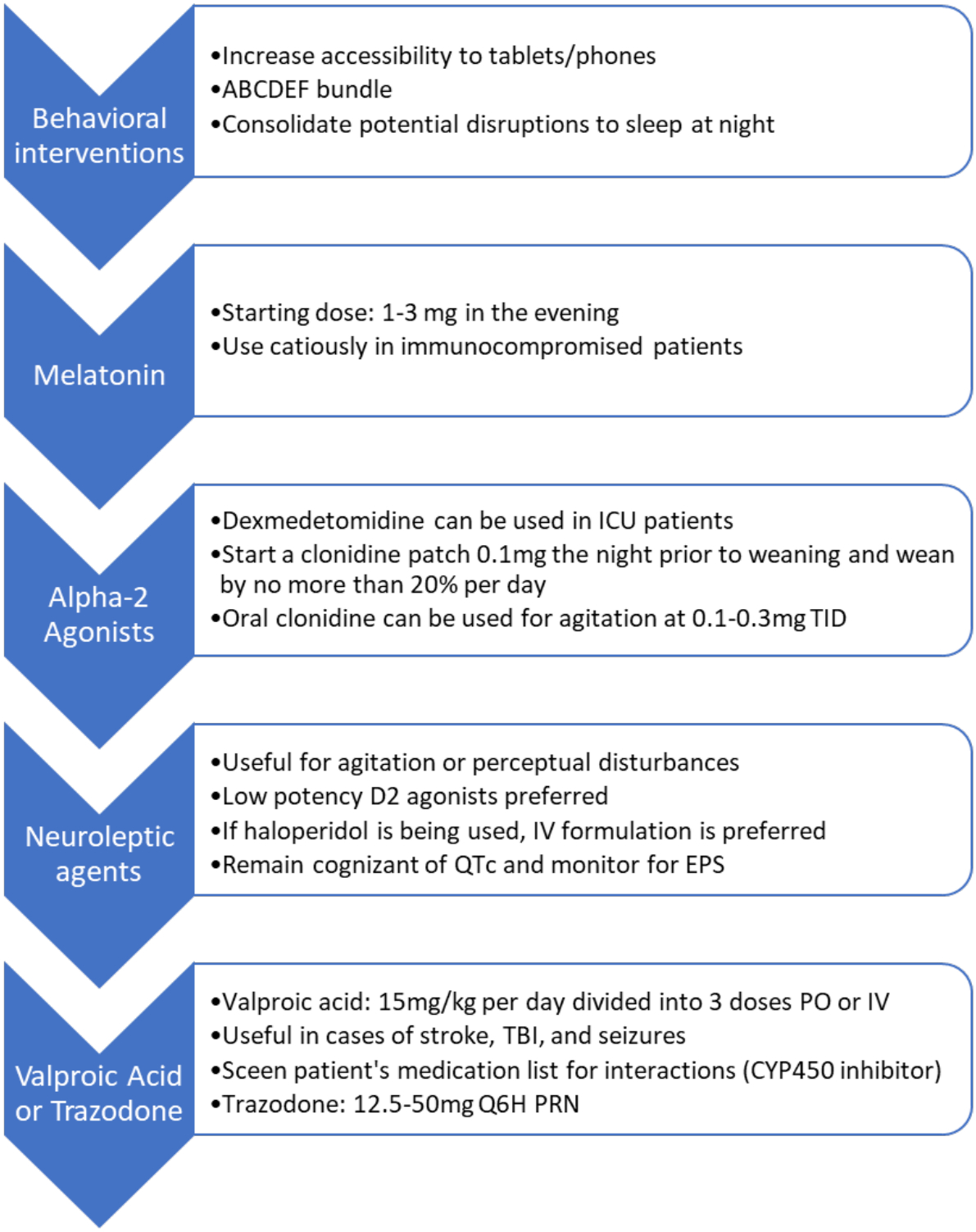
Though there are no Food and Drug Administration-approved treatments for COVID-19 delirium, a number of treatment guidelines have been proposed. Two protocols, developed early in the pandemic via expert consensus and anecdotal experience, provide a potential roadmap for management (Baller et

al., 2020; Sher et al., 2020). These protocols extrapolate data from non-COVID-19 delirium and incorporate unique features of the clinical exam. The majority of COVID-19 patients with delirium are recommended to be on melatonin. Production of melatonin is reduced in delirium, and in addition to regulating the sleep-wake cycle, the supplement has anti-inflammatory properties (Zhang et al., 2020). Caution is recommended only for severely immunocompromised patients who may not be mounting an adequate inflammatory response to COVID-19 and in whom melatonin could further suppress the immune response.

If the patient is hemodynamically stable, alpha-2 agonists should be considered. As noted above, dexmedetomidine, an alpha-2 agonist, is associated with lower rates of delirium. It can be weaned by up to 20% daily or cross-tapered to clonidine using a patch, which should be started the day prior to weaning (Baller et al., 2020). While antipsychotic agents are often used as a first line in the management of delirious patients, alpha-2 agonists may be chosen first in COVID-19-positive patients because of some potential for worsened EPS and additional QTc prolongation.

When choosing an antipsychotic agent, there are multiple factors to consider, including efficacy, routes of administration, and potential side effects. Olanzapine and chlorpromazine, both low-potency agents, have multiple formulations and allow for flexibility of administration as the patient's medical picture evolves. Though quetiapine also has lower risk of EPS, it is much more limited in regard to administration, as it is only available orally and has minimal D2 blockage at low doses. Ziprasidone, though helpful for treating psychosis and acute agitation, should also be avoided given the greater risk of QTc prolongation (Baller et al., 2020). Aripiprazole could be considered for hypoactive delirium with psychosis, though it carries high rates of akathisia and a very long half-life that potentially prevents the binding of other D2-blocking agents. If a patient has been confirmed to not have motor symptoms, intravenous haloperidol may be considered with close monitoring of the patient's neurologic exam. Though a high-potency antipsychotic, the intravenous formulation has been found to have reduced risk of EPS and minimal effects on blood pressure. It is also known to bind to the sigma receptor, which is thought to be immunoprotective (Gordon et al., 2020).

If an additional agent is needed or antipsychotics are contraindicated, valproic acid should be considered for the management of agitation, assuming the absence of hepatic or pancreatic disease. It may be preferred in patients with comorbid stroke, traumatic brain injury (TBI), or seizures. Given that it is a CYP450 inhibitor, psychiatrists and pharmacists should perform interaction checks when starting the medication. Trazodone, which has been found to be effective in the management of agitation in elderly populations, may be preferable in some cases for its lower risks of EPS, QTc prolongation, and respiratory depression. Use of benzodiazepines is generally associated with increased risk of delirium and should be avoided (Baller et al., 2020).



COVID-19 delirium treatment algorithm based on recommendations by Baller et al. (Baller et al., 2020).

Psychosis

Early in the pandemic, reports began emerging of patients developing symptoms of psychosis in the setting of acute COVID-19 infection. COVID-19-associated psychosis is now recognized as a rare but well-described phenomenon in the setting of acute infection. The quality of most literature remains poor, however, and is generally restricted to case reports and series. A series of retrospective studies, based on claims data and using other respiratory infections as a comparator and examining various neuropsychiatric outcomes, suggests that the risk of a new-onset psychotic disorder in the setting of COVID-19 infection remains elevated even 2 years after infection (Taquet et al., 2022; Taquet et al., 2021). In the more recent of those studies, the risk appears to be elevated most significantly for patients under age 18 and over age 65, with adults ages 18-65 showing no increased risk at 2 years (Taquet et al., 2022). An important limitation of the study design is ascertainment bias, as patients with COVID-19 infection and particularly those who were hospitalized may be followed more closely and more frequently assessed for comorbidities, including neurocognitive disorders that could be coded as psychosis.

Several reviews of case reports of COVID-19-associated psychosis, including two systematic reviews, have now been published and provide a sketch of the typical presentation of the phenomenon (O'Leary et al., 2023; Smith et al., 2021; Chaudhary et al., 2022). Approximately 55%–60% of cases have been reported in males, with an average age of 38–44 years (O'Leary et al., 2023; Smith et al., 2021). Symptoms of psychosis have lasted anywhere from 2 to 90 days, with delusions being the most commonly reported symptom, present in 92% of patients (Smith et al., 2021). In one systematic review, 23% of patients had significant medical comorbidities, 15% had premorbid mental illness, and 13% had substance use issues, numbers that are lower than would be expected for individuals with new-onset psychosis (Smith et al., 2021; Strakowski et al., 1993).

The differential diagnosis of COVID-19-associated psychosis is broad and includes delirium, a preexisting psychotic disorder, substance-induced psychosis (in the form of medications or illicit substances), and psychosis secondary to other medical conditions. Importantly, because symptoms of psychosis, including auditory and visual hallucinations, paranoia and delusions, and thought disorganization, can occur in the setting of delirium, the definition of COVID-19-associated psychosis requires that delirium be ruled out as a contributor (Watson et al., 2021). Notably, many case reports of new-onset psychosis in the setting of COVID-19 do not explicitly rule out or comment on delirium, suggesting that the incidence may be overreported. It is also generally agreed in the literature that COVID-19-associated psychosis involves a first episode of psychosis, affecting patients without a history of prior episodes of psychosis, as any acute infection may be a risk factor for the reemergence of psychosis in patients with a history of, for example, schizophrenia spectrum disorders. Further complicating the diagnostic assessment, patients with COVID-19-associated psychosis in case report literature have often received medications that are associated with psychosis, including corticosteroids, chloroquine derivatives, and the antiviral medication favipiravir. In evaluating possible cases of COVID-19-associated psychosis, such medications should be considered as causal, in addition to illicit substances associated with psychosis (e.g., cocaine, methamphetamine) and other medical conditions (e.g., hyperthyroidism, cerebrovascular disease). In older patients, it is also important to rule out major neurocognitive disorders, which may present with psychosis.

Also overlapping with psychosis, at least 23 cases of mania have been reported in the setting of acute infection with COVID-19 (Russo et al., 2022). Only 4 of these patients had a premorbid history of depression, and the mean age was 44 (Russo et al., 2022). In a systematic review of cases of COVID-19-associated psychosis, 17% of cases also had features of mania (Smith et al., 2021). The latency between

COVID-19 infection and the onset of mania averaged 12 days in the reported cases (Russo et al., 2022). Similar to cases of psychosis, these reports are confounded by other factors, including the administration of corticosteroids.

Given the low quality of the literature as well as the broad differential diagnosis and multiple confounding factors, it is important to keep in mind that the current evidence supports an association between acute infection with COVID-19 and new-onset psychosis but does not establish that COVID-19 infection causes psychosis. Some presentations of psychosis in the setting of recent COVID-19 infection may be coincidental, and other factors, including psychosocial stressors associated with infection, may also increase the risk for psychosis. Nonetheless, there are several intriguing potential pathways through which COVID-19 infection could lead to psychosis. At least one novel autoantibody has been isolated from a patient with new-onset psychosis in the setting of COVID-19, and molecular mimicry has been thought to play a role in several cases of NMDA-receptor-antibody encephalitis presenting with psychosis shortly following an acute COVID-19 infection (McAlpine et al., 2023; Vasilevska et al., 2021). Cases of seronegative autoimmune encephalitis in the setting of recent COVID-19 infection are also emerging, many of which have psychosis as a presenting symptom (Samim et al., 2022).

Regarding treatment of COVID-19-associated psychosis, many patients appear to respond well to standard antipsychotic agents, often with resolution of psychotic symptoms more quickly than would be expected in a typical first episode (Chaudhary et al., 2022). Given a risk for catatonia in the setting of COVID-19, low-potency, atypical agents such as olanzapine or aripiprazole may be preferred.

In addition to being aware of the potential for new-onset psychosis in the setting of COVID-19, psychiatrists should also keep in mind that patients with serious mental illness, including schizophrenia, are at increased risk for contracting COVID-19, for experiencing significant medical complications of the infection, and for experiencing psychotic exacerbations in the setting of acute illness (Fond et al., 2023). Furthermore, clozapine levels may increase dramatically in the setting of any acute infection, including COVID-19, due to the inhibition of cytochrome 1A2 (Dotson et al., 2020). A consensus statement therefore recommends very close monitoring for clozapine toxicity in patients with COVID-19, with dose reduction of up to 50% if signs of toxicity emerge (Siskind et al., 2020).

Catatonia and Related Syndromes

Catatonia has been described previously in the setting of viral illnesses, most famously as encephalitis lethargica during the influenza pandemic in 1918 (Scheiner et al., 2021). Early in the COVID-19 pandemic, reports began emerging of cases of catatonia and catatonia-like syndromes in the setting of acute COVID-19 infection (Caan et al., 2020). Around the same time, others described features of catatonia, including mutism, immobility, and withdrawal, occurring in delirious patients hospitalized with COVID-19 (Beach et al., 2020). Catatonia is now a well-recognized sequela of acute COVID-19 infection, with over 50 cases reported in the literature thus far. A study using the National Inpatient Sample found that 3.7% of catatonia cases identified at hospital discharge in 2020 involved co-occurring COVID-19, and catatonia was diagnosed in 0.04% of hospitalizations for COVID-19, with a total of 610 patients diagnosed with both catatonia and COVID-19 (Luccarelli et al., 2022). Patients with catatonia in the setting of COVID-19 have significantly longer lengths of stay compared to COVID-19-positive patients without catatonia (11 vs. 5 days, respectively). Notably, though catatonia has largely been seen in the acute phase of COVID-19 infection, one review found that it was even reported in the subacute phase and as a long-term complication (Dawood et al., 2022).

Of the patients identified as having catatonia in the setting of COVID-19 in a 2022 scoping review, approximately 40% were over age 50 and nearly 50% had preexisting psychiatric illness, including more than 25% with a known schizophrenia spectrum illness (Dawood et al., 2022). In a different study, 20% also received a discharge diagnosis of metabolic encephalopathy, 13% of unspecified encephalopathy, 12% of delirium, and 11% of toxic encephalopathy, suggesting that co-occurring delirium was highly prevalent (Luccarelli et al., 2022).

Presentation of catatonia in the setting of COVID-19 largely mimics that of catatonia more generally. The DSM-5-TR defines catatonia as requiring the presence of 3 or more of the following: waxy flexibility, negativism, grimacing, stereotypies, catalepsy, stupor, echolalia, echopraxia, agitation, posturing, mutism, and mannerisms. The Bush-Francis Catatonia Rating Scale (BFCRS), the most widely used scale for diagnosing and tracking catatonic symptoms, requires 2 of 13 symptoms to be present. In a scoping review, the BFCRS was used to diagnose 24% of the COVID-19 patients found to have catatonia, with scores ranging from 7 to 27 and a median score of 17 (Dawood et al., 2022). One important feature of catatonia in the setting of COVID-19 appears to be the frequent presence of co-occurring delirium. While the DSM-5-TR states that delirium and catatonia cannot simultaneously be diagnosed, clinical practice indicates that delirium is present in approximately one-third of patients with catatonia, particularly those who have catatonia due to a neuromedical illness (Luccarelli et al., 2022; Grover et al., 2014). As noted in the Delirium section, features of catatonia, including hypertonia, withdrawal, abulia, and alogia, have been frequently observed in delirious patients with COVID-19, suggesting some likely overlap (Beckwith et al., 2023). One systematic review also found that pro-inflammatory markers (D-dimer, platelet count, lymphocyte count, lactate dehydrogenase, ferritin, CRP, procalcitonin) were elevated in 7 out of 10 cases of COVID-19-related catatonia and that anxiety was a notable symptom in patients in 6 of the publications reviewed (Scheiner et al., 2021).

The differential diagnosis of catatonia should always include entities such as locked-in syndrome, minimally conscious and persistent vegetative states, parkinsonism, seizures, and malignant hyperthermia. In the setting of COVID-19, a particularly important set of syndromes to consider are the amotivation syndromes, with akinetic mutism (AM) representing the extreme of this spectrum. Cases of AM are now well described in the setting of COVID-19—one study estimated 13% of hospitalized COVID-19 patients exhibited AM (Nersesjan et al., 2021)—with clinical features overlapping significantly (Fusunyan et al., 2021). C. Miller Fisher described AM as a pure motor catatonia, as it typically lacks the affective (i.e., fear) and behavioral (e.g., stereotypies, mannerisms) features (Fisher, 1989). Risk factors for AM in COVID-19 appear to include severe respiratory illness, meningoencephalitis, and preexisting neuropsychiatric vulnerability (Fusunyan et al., 2021). The distinction is important because, unlike catatonia, AM does not typically respond to benzodiazepines and cases typically last 1–2 weeks (Fusunyan et al., 2021).

The pathophysiology of catatonia in the setting of COVID-19 remains unclear. Some have noted that extreme systemic inflammatory responses, as have been observed in the setting of acute COVID-19 infection, may lead to states of dopamine depletion in the brain, which conveys a vulnerability to catatonia, as when a patient is administered a dopamine-blocking agent (Beach et al., 2020). Immune dysregulation has also been hypothesized to be central to catatonia in general (Rogers et al., 2019; Beach et al., 2023). One evolutionary-based hypothesis regarding catatonia in general is that it represents an extreme fear response, akin to lower mammals playing dead (Moskowitz, 2004). Finally, it has been observed that many patients with COVID-19-associated catatonia have comorbid delirium or psychosis. Catatonia is prominent in hypoactive delirium in general, with some studies estimating that up to one-third of patients with delirium exhibit features of catatonia (Grover et al., 2014). Perhaps the

same process that leads to delirium in COVID-19 also causes catatonia. Similarly, many of the pathophysiological mechanisms proposed to account for psychosis in the setting of COVID-19 may also apply to catatonia.

Most cases of COVID-19-associated catatonia have responded to traditional treatments for catatonia, including benzodiazepines. In one series, lorazepam was successful in over 80% of the cases in which it was used (Dawood et al., 2022). Many cases that have not responded to benzodiazepines have been successfully treated with electroconvulsive therapy (Dawood et al., 2022). Some patients deemed to have an underlying encephalitis have also responded to treatment with steroids or immunotherapies (Dawood et al., 2022).

Workup for Patients with COVID-19

Given that the World Health Organization now considers altered mental status to be a core symptom of acute infection, and given one study suggesting it as the 6th most common presenting symptom (with 37% of patients presenting with altered mental status in the setting of COVID-19 infection not exhibiting other symptoms) (Kennedy et al., 2020), all patients presenting with altered mental status should undergo testing for COVID-19. Basic blood work, including a metabolic panel and complete blood count, is recommended for all patients with COVID-19, with consideration given to including markers of inflammation, such as CRP. For patients presenting with delirium in the setting of acute infection, an EEG and a lumbar puncture are not routinely recommended in the absence of specific relevant findings. Imaging in the form of MRI may be useful, particularly for older patients in order to rule out CVA, subdural hematoma, and neurodegenerative processes. In all cases, the utility of testing should be weighed against the additional exposure risks, though these tend to be minimal at this stage in the evolution of COVID-19 when personal protective equipment is widely available.

For patients presenting with new-onset psychosis, mania, or catatonia, a full workup is recommended, as would be standard for any patient presenting with a first episode of these conditions. Given the possibility of molecular mimicry, strong consideration should be given to obtaining an autoimmune encephalitis panel from these patients. Iron studies should be obtained for any patient presenting with catatonia given evidence that low iron constitutes a risk factor for catatonia and for conversion to malignant catatonia.

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