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Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms

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ABSTRACT

The coronavirus disease 19 (COVID-19) pandemic is a significant psychological stressor in addition to its tremendous impact on every facet of individuals' lives and organizations in virtually all social and economic sectors worldwide. Fear of illness and uncertainty about the future precipitate anxiety- and stress-related disorders, and several groups have rightfully called for the creation and dissemination of robust mental health screening and treatment programs for the general public and front-line healthcare workers. However, in addition to pandemic-associated psychological distress, the direct effects of the virus itself (several acute respiratory syndrome coronavirus; SARS-CoV-2), and the subsequent host immunologic response, on the human central nervous system (CNS) and related outcomes are unknown. We discuss currently available evidence of COVID-19 related neuropsychiatric sequelae while drawing parallels to past viral pandemic-related outcomes. Past pandemics have demonstrated that diverse types of neuropsychiatric symptoms, such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, may accompany acute viral infection, or may follow infection by weeks, months, or longer in recovered patients. The potential mechanisms are also discussed, including viral and immunological underpinnings. Therefore, prospective neuropsychiatric monitoring of individuals exposed to SARS-CoV-2 at various points in the life course, as well as their neuroimmune status, are needed to fully understand the long-term impact of COVID-19, and to establish a framework for integrating psychoneuroimmunology into epidemiologic studies of pandemics.

1. Introduction

The coronavirus disease 19 (COVID-19) pandemic continues to grow, and as of April 9, 2020, more than 1.5 million cases have emerged globally. The United States is now the most affected country, surpassing 450,000 cases according to the Johns Hopkins University & Medicine Coronavirus Resource Center (https://coronavirus.jhu.edu/map.html). Fears of illness, death, and uncertainty of the future are significant psychological stressors for the population, and social isolation resulting from loss of structured educational and work activities also threatens to worsen public mental health (de Carvalho et al., 2020). For front-line healthcare workers, regular exposure to the illness, protective equipment shortages, and adaptation to rapidly evolving and high-stress work environments are further sources of distress (Joob and Wiwanitkit, 2020; Kang et al., 2020a). This pandemic is a potential source of direct and vicarious traumatization for everyone (Li et al., 2020b), which is only further emphasized by unsettling case reports of suicide deaths related to fears of contracting or spreading COVID-19 (Goyal et al., 2020; Montemurro, 2020). Therefore, several groups have rightfully called for the development and implementation of mental health screening and intervention programs for both the public and for healthcare workers (Bao et al., 2020; Xiang et al., 2020).

However, less attention has been given to the role of the virus itself (several acute respiratory syndrome coronavirus; SARS-CoV-2), and the host immunologic response to infection, on the human central nervous system (CNS) and related neuropsychiatric outcomes. Studies of past respiratory viral pandemics suggest that diverse types of neuropsychiatric symptoms can arise in the context of acute viral infection, or after variable periods of time post-infection. Reports from the 18th and 19th centuries suggest that influenza pandemics in particular have been marked by increased incidences of various neuropsychiatric symptoms, such as insomnia, anxiety, depression, mania, psychosis, suicidality, and delirium (Honigsbaum, 2013; Menninger, 1926). For instance, encephalitis lethargica (EL) is an inflammatory disorder of the

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CNS marked by hypersomnolence, psychosis, catatonia, and Parkinsonism, the incidence of which increased around the time of the "Spanish" influenza pandemic of the early 20th century (Von Economo, 1932). During the more recent 2009 influenza (H1N1) pandemic and other coronavirus infections (SARS-CoV-1 epidemic in 2003, and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012), several neuropsychiatric sequelae were reported, including narcolepsy, seizures, encephalitis, encephalopathy, Guillain-Barre syndrome (GBS), and other neuromuscular and demyelinating processes (Kim et al., 2017; Manjunatha et al., 2011; Tsai et al., 2004; Wu et al., 2014).

Reports are already surfacing of acute CNS-associated symptoms in individuals affected by COVID-19 (Mao et al., 2020), the neurologic manifestations and mechanisms of which were recently discussed in *Brain, Behavior, Immunity* (Wu et al., 2020b). However, beyond acute infection, the delayed or chronic effects of this pandemic, particularly on public mental health, will not be fully appreciated for several years. Thus, timely and longitudinal investigations of potential COVID-19 associated neuropsychiatric outcomes are critical in disease surveillance and evidence-based therapeutic strategies. Here we review the available studies of acute neuropsychiatric symptoms in the context of COVID-19 for timely evaluation of the evidence. Furthermore, we postulate possible delayed post-viral sequelae of COVID-19 based on findings from other coronavirus or past viral pandemics. Lastly, potential mechanisms by which neuropsychiatric symptoms could develop, especially, in the context of immune reactions to viral illness are discussed, as are future directions.

2. Acute neuropsychiatric symptoms associated with SARS-CoV-2 infection

The evidence of acute neuropsychiatric symptoms in COVID-19 cases is emerging. An initial report of 217 hospitalized patients in Wuhan, China, described neurologic manifestations in nearly half of those with severe infection (40 of 88), including cerebrovascular complications (e.g., stroke), encephalopathies, and muscle injuries (Mao et al., 2020). Interestingly, total blood lymphocyte counts were significantly lower in patients with CNS-associated (e.g. headache, dizziness, ataxia) or muscular (e.g., myalgia) symptoms, and the latter group also exhibited elevated plasma C-reactive protein (CRP) relative to patients without muscular involvement. Immunologic findings in COVID-19 patients with neurologic symptoms are in line with prior CoV-related findings, describing significantly reduced blood lymphocyte counts in CoV-positive children with encephalitis (CoV-CNS) compared to those with acute respiratory CoV-associated infection (Li et al., 2017), and when considered in conjunction with circulating CRP levels or neutrophil counts may be prognostic of poorer COVID-19 outcomes (Lagunas-Rangel, 2020). It is unknown if reduced lymphocytes in circulation reflect margination or target tissue migration, although probable. Plasma granulocyte macrophage colony-stimulating factor (GM-CSF) levels were significantly higher in CoV-CNS patients (Li et al., 2017), which may drive the expansion of CNS-invading phagocytes (e.g., inflammatory monocyte-derived cells; MdC such as dendritic cells) (Zhao et al., 2017). In fact, GM-CSF has emerged as a potential biological target in treating severe COVID-19 (Zhou et al., 2020); this may mitigate neuropsychiatric sequelae by limiting MdC neuroinvasion.

2.1. Encephalopathies

A retrospective report of COVID-19 patients from Wuhan described encephalopathy, or persistent (> 24 h) alterations in consciousness, in roughly one-fifth of individuals succumbing to the disease (Chen et al., 2020). Notably, blood plasma levels of pro-inflammatory cytokines (e.g., interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, IL-8, IL-10, IL-2R) were significantly higher among fatal COVID-19 cases, indicative of hypercytokinemia, or "cytokine storm syndrome," which was also reported in SARS-CoV-1 (Huang et al., 2005), and may underlie encephalopathy. Beyond the acute effects of cytokine storm, a recent meta-analysis of delirium among intensive care patients of mixed conditions reported evidence of persistent neurocognitive deficits up to 18 months post-discharge (Salluh et al., 2015), including mild cognitive impairment (Chung et al., 2020). Given other emerging evidence of hypercytokinemia in hospitalized COVID-19 patients (Yang et al., 2020), the burden of long-term post-SARS-CoV-2 delirium may be significant, particularly for elderly patients who are more susceptible to post-infectious neurocognitive complications.

2.2. Anosmia and ageusia

Newly emerging reports indicate that SARS-CoV-2 infection is associated with dysfunction of olfaction and taste perception, which may be among the earliest symptoms in an unknown proportion of confirmed cases. Prior experimental studies of coronavirus have demonstrated that infection with human alphacoronavirus (HCoV-229E) disrupts ciliary nasal epithelium (Chilvers et al., 2001), a possible mechanism of olfactory dysfunction. Indeed, olfactory epithelial cells express the CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), yet the precise cellular subtype that may mediate anosmia in COVID-19 remains unclear (Brann et al., 2020). For both olfactory and gustatory perception, CoV-2 infiltration of higher-order structures within the CNS, or cranial nerves such as the vagus nerve, involved in signal transduction and chemosensory processing, may underlie their dysfunction (Bromley, 2019). Although studies on post-viral olfactory disorders (PVOD) exist for influenza and other viruses, only a single case report describes persistent coronavirus-associated (SARS-CoV-1) anosmia (Hwang, 2006). Formal studies have yet to be published for CoV-2-related anosmia in spite of a growing number of clinical cases (Vaira et al., 2020); however, it has emerged as a screening criterion for COVID-19 at a growing number of clinics. Whether acute anosmia during the initial phase of infection, as reported in COVID-19, will also be associated with PVOD is currently unknown.

3. Sub-acute to chronic neuropsychiatric sequelae of SARS-CoV-2 infection

Long-term neuropsychiatric complications following SARS-CoV-2 infection are currently unknown and remain to be seen over the next several months to years. Following past influenza pandemics and CoV outbreaks, such complications have been described over highly variable periods of time, from weeks following acute respiratory symptoms in the case of neuromuscular and demyelinating processes, to decades after in-utero exposure to viral infection in the case of schizophrenia onset (Kępińska et al., 2020; Kim et al., 2017; Tsai et al., 2004). Given the global burden of COVID-19 infection, even if delayed neuropsychiatric sequelae are associated with a fraction of cases, the public health implications of such complications will be significant. Thus, understanding the trajectory and characteristics of neuropsychiatric outcomes stemming from CoV-2 infection and uncovering pathogenic mechanisms that can inform targeted interventions will be critical.

3.1. Depression, anxiety, and trauma-related disorders

Depression, anxiety, and trauma-related symptoms have been associated with CoV outbreaks, but it remains unclear whether the risks are attributable to viral infections per se or the host immune response. Studies of healthcare workers during the SARS-CoV-1 epidemic, MERS-CoV outbreak, and the current SARS-CoV-2 pandemic suggest that the frequency and severity of psychiatric symptoms are associated with proximity to CoV-infected patients (Kang et al., 2020b; Lai et al., 2020; Lee et al., 2018; Lin et al., 2007). However, these studies did not test serology or immune markers in healthcare workers, and no studies have

been performed comparing psychiatric outcomes in healthcare workers who contracted CoV during pandemics versus those who did not. Separately, seropositivity for a human CoV strain (HCoV-NL63) has been associated with history of mood disorder, although not with its polarity (i.e. unipolar versus bipolar depression) or with history of suicide attempts (Okusaga et al., 2011). Although there are very limited data available for COVID-19-related psychiatric symptoms currently, survivors of SARS-CoV-1 were clinically diagnosed with PTSD (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) at 31 to 50 months post-infection, a dramatic increase from their pre-infection prevalence of any psychiatric diagnoses of 3% (Lam, 2009). The need for sustained follow-up of such symptoms related to SARS-CoV-2 infection, beyond documenting acute stress levels, is therefore paramount and urgent.

3.2. Psychotic disorders

Exposure to viral infections in utero, during childhood development, and in adulthood have each been associated with increased risk of developing schizophrenia (Brown and Derkits, 2010; Khandaker et al., 2012; Menninger, 1926). While most studies have focused on history of influenza infection and psychosis risk, two studies have evaluated presence of antibodies against several strains of coronavirus in individuals with psychosis. No association was reported between seropositivity for HCoV-NL63 and history of psychotic symptoms in mood disorder patients in one study (Okusaga et al., 2011). However, Severance and colleagues (2011) found increased prevalence of antibodies against four HCoV strains in patients with a recent psychotic episode compared to non-psychiatric controls (Severance et al., 2011), suggesting a possible relationship between CoV infections and psychosis, which may also occur in SARS-CoV-2.

3.3. Demyelinating and neuromuscular complications

Delayed neurologic sequelae have been described following both SARS-CoV-1 and MERS-CoV infection, such as peripheral neuropathy, myopathy, Bickerstaff brainstem encephalitis (BBE), and Guillain-Barre syndrome (GBS), and these symptoms were reported to occur two to three weeks after respiratory symptoms (Kim et al., 2017; Tsai et al., 2004). These post-CoV complications were described in small case series, and causality therefore, cannot be definitively established. Separately, murine CoVs are neuroinvasive and precipitate demyelination (Lane and Hosking, 2010). In humans, postmortem analysis of brain tissue from multiple sclerosis (MS) patients and controls indicated that HCoV RNA was present in 48% of all donors, with a greater incidence of OC43, but not 229E strain, in MS patients (Arbour et al., 2000). These findings suggest that although HCoV infiltration into the CNS is prevalent, its association with demyelinating disorders such as MS may be strain-specific. Whether recovered SARS-CoV-2 patients will exhibit an increased incidence of MS symptomatology or other delayed neurologic sequelae, is an important, yet unanswered, question that necessitates surveillance.

3.4. Neurodegenerative disorders

Parkinsonism is a late feature of encephalitis lethargica, which was first described following the influenza pandemic of 1918 (Cheyette and Cummings, 1995). While features of Parkinsonism and Parkinson's disease (PD) have not been described in association with CoV pandemics or outbreaks, anti-CoV antibodies have been identified in cerebrospinal fluid (CSF) of individuals with Parkinson's disease (Fazzini et al., 1992). Given that neural and immune cells can serve as reservoirs of latent CoV, it is plausible that this could contribute to delayed neurodegenerative processes (Desforges et al., 2019), but this also, remains to be seen in COVID-19.

4. Potential mechanisms of neuropsychiatric manifestations in COVID-19

4.1. Viral infiltration into the central nervous system

The neuroinvasive potential of CoV has been reported in SARS-CoV-1 patients and experimental animals, and spread from the respiratory tract to the CNS could occur via retrograde axonal transport from peripheral nerves such as the olfactory nerve, or via hematogenous spread (Desforges et al., 2019). After entering the CNS, CoV has been shown to induce neuronal cell death in mice (Netland et al., 2008). Further, mice infected with HCoV-OC43 develop chronic encephalitis, marked by viral persistence in neurons and behavioral abnormalities (Jacomy et al., 2006). It has been speculated that the neuroinvasive potential of SARS-CoV-2, particularly of medullary structures involved in respiration (e.g., solitary tract nucleus, nucleus ambiguus), may partially mediate the high incidence of respiratory failure currently seen in COVID-19 (Li et al., 2020a), which requires further investigation. Recent articles also, discuss routes and mechanisms of CoV neurotropism (Vavougios, 2020; Wu et al., 2020b).

4.2. Cytokine network dysregulation

One challenge to elucidating the mechanisms of COVID-19-associated neuropsychiatric complications is that SARS-CoV-2 encephalitis, or CNS inflammation as evidenced by fever, focal neurologic signs, cerebrospinal fluid (CSF) pleocytosis, neuroimaging, and electroencephalogram (EEG) findings, may be difficult to distinguish from encephalopathy arising from systemic (but not CNS) infection. At present, only one study to our knowledge has identified SARS-CoV-2 RNA in CSF of a COVID-19 patient with acute neurologic symptoms, including seizures (Moriguchi et al., 2020), although case reports of CoV detection in CSF among patients during the previous SARS-CoV-1 epidemic do exist (Lau et al., 2004). Two recent case reports of severe COVID-19 indicate meningitic and/or encephalitic pathology in the absence of viral RNA detection in CSF, which the authors suggest could be associated with transient or low viral load in the CNS, or due to lack of availability of testing (Duong et al., 2020; Ye et al., 2020). Notably, the key receptor that SARS-CoV hijacks for host intracellular invasion (ACE2) is expressed in both neurons and glia, and experimental studies of intranasally-inoculated SARS-CoV-1 infection in ACE2 transgenic mice demonstrated neuronal death and upregulation of proinflammatory cytokine secretion (e.g., TNF-alpha, IL-1-beta, IL-6) by neurons and astrocytes (Netland et al., 2008). Even in the absence of CoV-2 infiltration into the CNS, peripheral cytokines involved in the host anti-viral response (see Section 2.1) may elicit neuropsychiatric symptoms by precipitating neuroinflammatory responses and/or compromised blood–brain-interface (BBI) integrity, leading to peripheral immune cell transmigration into the CNS, and disruption of neurotransmission (Dantzer, 2018).

4.3. Peripheral immune cell transmigration

Peripheral myeloid cells are infected by CoV (Desforges et al., 2019), and can subsequently be recruited or transmigrate to the CNS under conditions which increase blood brain barrier (BBB) permeability, such as inflammation or psychological stress. In the CNS, virus-infected monocytes can propagate neuroinflammation, and therefore neuropsychiatric symptoms, by releasing inflammatory cytokines, and by promoting microglial activation (Hong and Banks, 2015; Wohleb et al., 2015). There is also evidence suggesting that leukocytes can remain persistently infected by CoV (Arbour et al., 2000; Desforges et al., 2007). Therefore, it can be speculated that the time-course over which CoV-infected immune cells could serve as a potential source of neuroinflammation could be significantly longer than the initial infection and acute symptom presentation.

4.4. Post-infectious autoimmunity

Autoimmune disorders of the nervous system, such as BBE and GBS, have been described following SARS-CoV-1 and MERS-CoV (Kim et al., 2017; Tsai et al., 2004). Viral infections may precede development of autoimmunity in vulnerable individuals. The underlying mechanisms may include viral infection creating an inflammatory milieu which favors aberrant immune responses and promoting expansion of host antibodies or lymphocytes, which are cross-reactive both with viral antigen and self-antigen (i.e. "molecular mimicry") (Fairweather et al., 2005; Rose, 2017). In animal models of MS, auto-reactive lymphocytes have been identified which cross-react with both CoV epitopes and human myelin (Desforges et al., 2019), suggesting that molecular mimicry might be a potential mechanism by which CoV infection could potentiate development of autoimmune neuropsychiatric sequelae.

4.5. Immunomodulatory treatments

A subset of COVID-19 cases are associated with a hyperinflammatory response, and immunomodulatory therapies have therefore been proposed in the treatment of severe cases (Mehta et al., 2020). The clinical efficacy of corticosteroids in treating COVID-19 is currently unclear, with some groups advising against their use (Russell et al., 2020). However, retrospective studies suggest corticosteroids are not uncommonly used to treat hospitalized COVID-19 patients (Liu et al., 2020; Mo et al., 2020; Wan et al., 2020). Similarly, high doses of corticosteroids were administered to treat SARS CoV-1 infection symptoms during the acute phase (Lee et al., 2003), but were associated with organic hallucinations and manic symptoms, which were treated with haloperidol (Cheng et al., 2004). There is ample evidence of adverse neuropsychiatric effects following corticosteroid therapy, impacting about 35% of treated patients, including cognitive and sleep disturbances, delirium, hypomania, mania, depression, and psychosis (Brown and Chandler, 2001; Warrington and Bostwick, 2006). The neuropsychiatric effects of corticosteroid treatments are typically acute and resolve upon termination of treatment, suggesting that steroid-mediated neuropsychiatric symptoms among COVID-19 cases will likely be acute, but necessitate close monitoring and intervention as needed, nonetheless. Further, other immunomodulatory treatments have been proposed for treating severe COVID-19, including intravenous immunoglobulin (IVIG), cytokine blocking medications, and Janus kinase (JAK) inhibitors (Mehta et al., 2020). However, the degree to which these agents have been used clinically, and the neuropsychiatric outcomes in infected individuals who have been exposed versus not exposed to such treatments, are unknown, highlighting the need for further investigation going forward.

4.6. Gut microbial translocation

Viral shedding in feces of COVID-19 patients is known to occur for at least five weeks post-infection (Wu et al., 2020a). Although the extent and mechanisms of viral infiltration of gut epithelium by SARS-CoV-2 are currently unknown, ACE2 is expressed by gut epithelial cells, and almost 40% of COVID-19 patients present with gastrointestinal (GI) symptoms (Zhang et al., 2020). As such, gastroenterologists performing fecal microbiota transplantation (FMT) to treat *C. difficile* have identified the need to screen donors for potential GI infiltration by SARS-CoV-2 (Ianiro et al., 2020). It may be the case that SARS-CoV-2 infection precipitates changes in gut microbial composition, which could be involved in the pathogenesis of neuropsychiatric symptoms via the gut-brain axis; this remains largely speculative, but is mechanistically feasible (Li et al., 2019).

5. Conclusions

COVID-19 is projected to affect a remarkably high proportion of the global population, which is unprecedented for a virus with such case fatality and infection rates in modern medicine. Nevertheless, the neuropsychiatric burden of this pandemic is currently unknown, but likely to be significant. Past pandemics of this magnitude occurred tens to hundreds of years ago; therefore, epidemiologic associations between viral infection and neuropsychiatric symptoms were noted, but causality and etiopathogenic mechanisms were not well elucidated. In more recent CoV outbreaks, neuropsychiatric symptoms have generally been underexplored relative to respiratory and other symptoms. The breadth of the current SARS-CoV-2 pandemic will likely require closer examination of the mechanisms underlying, and the interventions for, post-viral neuropsychiatric sequelae, which will likely be heterogeneous and extensive.

We urge the biomedical community's attention to the needs of longitudinal monitoring of neuropsychiatric symptoms and neuroimmune status in individuals exposed to SARS-CoV-2 at different time points across the life course, including in utero, throughout childhood development, in adulthood, and in advanced age, to fully appreciate and mitigate the long-term deleterious impacts of COVID-19 on brain and behavior. Thus, a psychoneuroimmunology perspective will be invaluable in tackling this rapidly developing public health crisis.

Disclosure statement

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