Chapter

Chronic Mild Stress and COVID-19 Sequelae

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Abstract

Although COVID-19 clinical presentation primarily involves the respiratory system causing bilateral pneumonia, it is becoming increasingly recognized that COVID-19 is in fact a systemic disease. Neurological presentations have been reported in patients with both mild and severe COVID-19 symptoms. As such, elderly individuals are at a significantly higher risk of developing severe COVID-19 as well as neurocognitive consequences due to the presence of comorbidities associated with aging and the direct consequences of infection. Several neurological disorders that have been described in the literature include insomnia, depression, anxiety, post-traumatic stress disorder and cognitive insufficiencies. The potential underlying mechanisms are still incompletely understood but are likely multifaceted, involving both direct neurotrophic effect of SARS-CoV-2 and the indirect consequences related to social isolation in long intensive care units, the use of mechanical ventilation and sedation and the resultant brain hypoxia, systemic inflammation and secondary effects of medications used in treatment of COVID-19. Furthermore, neuro-cardiovascular adaptations resulting from the chronic stress and depression milieu of COVID-19 is expected to contribute negatively to the cardiovascular health of the survivors. It is thus imperative to implement a rigorous monitoring program for COVID-19 survivors, particularly among the elderly population, to assess potential neuro-cognitive and cardiovascular deteriorations.

Keywords: COVID-19, neuroinflammation, chronic stress, depression, cardiovascular disease

1. Introduction

Since the unfolding of COVID-19 pandemic starting in early 2020 it has become increasingly apparent that the disease has evolved from primarily affecting the respiratory system to being a systemic disease. A common manifestation of the latter involves the neurologic system, ranging from headache and myalgia to neuroinflammation and encephalopathies. Additionally, neuropsychiatric manifestations such as anxiety, stress, depression and post-traumatic stress disorder (PTSD) have been reported [1–4]. Another common manifestation affects the cardiovascular system, with pathologies ranging from pericarditis, myocarditis, right-hearted dysfunction, enodothelialitis and prothrombotic state (as reviewed in [5]). Any potential long-term

effects of these disorders are yet to manifest in the coming months and years. Based on the available data, the interactions among chronic mild stress, neurological consequences and cardiovascular manifestations due to COVID-19 pandemic are likely to contribute to a significant public health problem worldwide. These interactions are explored below throughout the chapter.

Stress, depression and anxiety are being recognized as risk factors for the development of cardiovascular disease (CVD). COVID-19 pandemic has induced many stressors on everyday life, including fear of infection, lack of social interactions due to quarantine, helplessness due to inevitability, loss of income, misinformation spread mostly by social media, and food and household item shortage. Furthermore, the viral infection itself can cause detriment to the cardiovascular system via cerebrovascular ischemia, coagulopathy and endothelial dysfunction. Therefore, both individuals who become infected and those who do not, but are exposed to the chronic mild stress (CMS) of COVID-19 pandemic may be at risk of developing neurologic and cardiovascular consequences (please see a model in **Figure 1**). In any event, the stressors of the pandemic can be modeled by the CMS rodent model of depression. The CMS paradigm is typically conducted for 4 weeks and consists of the exposure of rodents to mild stressors such as exposure to strobe light and white noise, acute withdrawal of water, damp bedding and social isolation [6–9]. This procedure causes depression as evidenced by anhedonia (in rodents manifested as reduced 1–2% sucrose solution consumption and spontaneous wheel running), circadian rhythm disturbances and demeanor. This rodent model of human depression was used extensively to demonstrate the cardiovascular dysfunction following 4 weeks of exposure to the mild stressors, characterized by increased mean arterial pressure and sympathetic nervous system activity and decreased heart rate variability [6, 7, 9]. One study found that the 4 week period of stress exposure followed by 4 week period of stress reduction (i.e. no exposure to stressors) recovered the behavioral manifestations of depressions, such as sucrose consumption and spontaneous wheel running, but did not result in the reversal of the cardiovascular dysfunction measured by heart rate variability [9]. Such long term effects of stress exposure, as is seen in the COVID-19 pandemic, could therefore be detrimental in the post-pandemic era, highlighting the importance of cardiovascular health monitoring in all individuals.

2. Cognitive and neuropsychiatric manifestations of COVID-19

Pandemics are considered to be one of the most devastating disaster types, since they have global consequences that particularly affect mental health. Although not of pandemic proportions, previous outbreaks of viral infections involving coronaviruses, SARS (SARS-CoV) and MERS (MERS-CoV), and other viruses such as Ebola and Zika, provided valuable insights into the potential devastating effects on mental health status [10, 11].

Multiple reports and meta-analyses described that most common neuropsychiatric manifestations of COVID-19 are insomnia, depression and anxiety, PTSD, and various psychoses. In terms of prevalence, almost one quarter (22.5%) of those infected were found to have experienced some neurological and/or psychiatric episodes among 40,469 patients of whom majority was in the United States [3]. Subsequent studies from Europe reported similar outcomes [12–14]. Critically ill

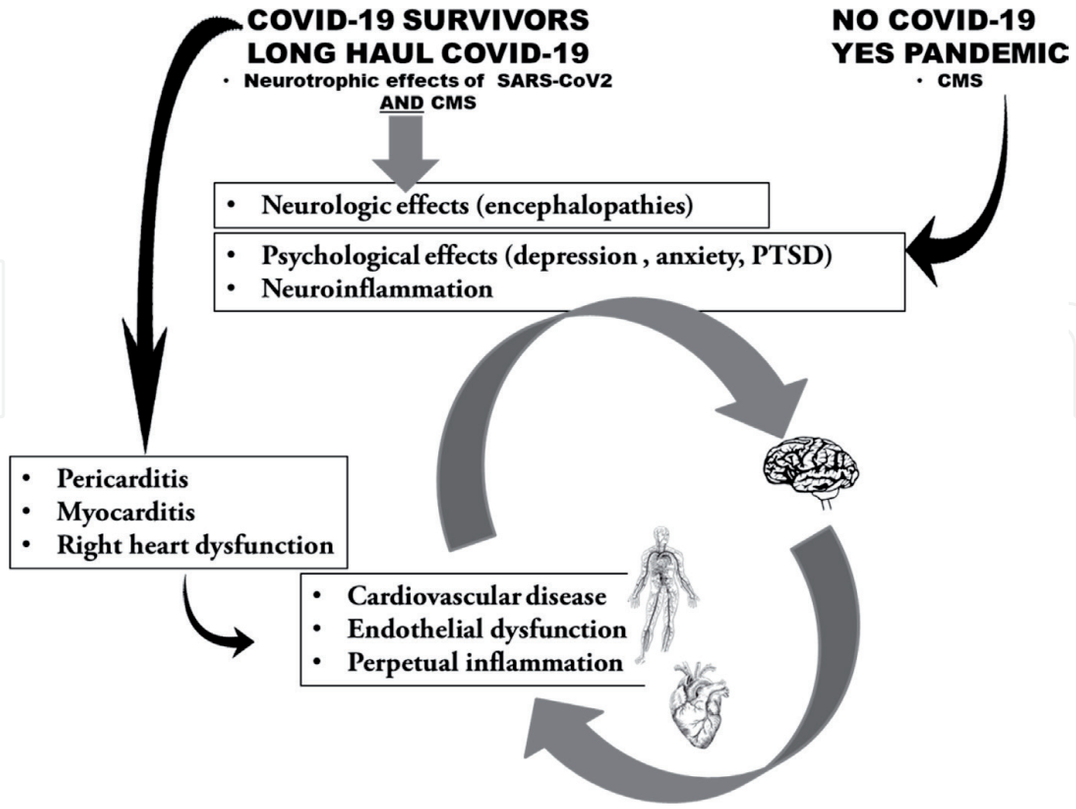

Figure 1.
Direct and indirect effects of COVID-19 on the central nervous and cardiovascular systems. Individuals who became infected with SARS-CoV2 virus could experience neurologic and cardiovascular dysfunction due to the direct neurotrophic effects of the virus as well as indirectly, via experiencing chronic stress associated with the pandemic (i.e. loss of loved ones, loss of income, lack of exercise, poor nutrition etc.). Individual who evaded infection, although spared from the direct effects of the virus, are also at an increased risk of developing neuropsychiatric and cardiovascular diseases via experiencing chronic stress associated with the pandemic. Therefore, those who survived COVID-19 and those who never got the disease but lived through the pandemic should be monitored both for mental health and cardiovascular health changes in the years to come.

individuals who required intensive care unit (ICU) admissions are particularly at risk of developing cognitive and neuropsychiatric manifestations, due to sedation, intubation, presence of comorbidities and older age [15–19]. One study from France reported that in a small cohort of 45 patients, 15 of them reported cognitive disturbances in form of dysexecutive syndrome (dysregulated movement patterns and lack of attention) at discharge from ICU [14]. Furthermore, almost half of them presented with confusion upon admission that was accompanied by brain hypoperfusion in several individuals revealed after brain imaging [14]. Depressive symptoms were also prevalent among individuals who recovered from COVID-19 in China [20–22]. Moreover, immune system suppression was evidenced in those with depressive symptoms indicated by increased white blood cell count and pro-inflammatory markers [21].

The impact of COVID-19 on one's neuropsychological well-being can be a direct result of SARS-CoV2 viral infection of the central nervous system (CNS) and/or an indirect result of endured psychological stress due to the devastating elements of the pandemic, such as fear of infection, social isolation, loss of income etc. The characteristic, mechanisms and implications of the first are detailed below throughout Section 2 of this Chapter, and those of the latter are elaborated on in Section 3 of this Chapter.

2.1 Mechanisms of cognitive and neuropsychiatric sequelae of COVID-19

Initially in early 2020, it was speculated but not confirmed that SARS-CoV2 is indeed a neurotrophic virus [23]. Shortly thereafter, the first case of viral encephalitis was reported in May of 2020 [24], making it obvious that the virus is capable of invading the CNS. Similar to other coronaviruses, SARS-CoV1 and MERS-CoV, SARS-CoV2 infection can cause CNS issues that range from mild such as loss of taste and smell (ageusia and anosmia, respectively), headache and dizziness, to very serious such as stroke, seizures, loss of balance and mental status alterations [25]. These consequences could result from: (i) the direct infection of neuronal cells by the virus, (ii) immune system dysregulation, (iii) autoimmunity resulting from the infection itself and/or (iv) any combination of the above three [26]. In addition to the direct invasion of neuronal cells, a secondary systemic mechanism could also be at play. This mechanism involves acute respiratory distress syndrome (ARDS). ARDS is accompanied by hypoxemia, oxidative stress and uremia resulting from multi-organ failure, including the cardiovascular system derangements and such complications could lead to encephalopathy. Immune system dysregulation may involve the cytokine storm and subsequent breakdown of the blood brain barrier (BBB) allowing entry of SARS-CoV2 into the CNS. This model is further supported by the fact that the virus binds ACE2 receptor that is present on capillary endothelium, thus leading to BBB damage and entry of the virus into the CNS [27]. Furthermore, immune system involvement could occur at the level of toll like receptors (TLRs), of which there are 10 identified members in humans, numbered 1–10 [28]. In particular, TLR 7/8 is recruited in response to single stranded RNA viruses, such as SARS-CoV2, leading to the production of pro-inflammatory mediators such as interleukin (IL)-1, IL-6, tumor necrosis factor alpha and interferon gamma [29]. Uncontrolled production of the pro-inflammatory mediators may lead to cytokine storm which causes ARDS, leading to encephalopathy secondary to an inflammatory response [30]. In another model, it was suggested that SRAS-CoV2 may operate similar to HIV in that HIV causes encephalopathy via a mixed approach: both directly via neuronal cell invasion and indirectly via the above discussed inflammatory mechanisms [26].

2.2 Potential long-term neuro-psychiatric effects: long haul COVID-19

The syndrome of persistent symptoms associated with COVID-19 that extend beyond the period of initial infection was originally termed long haul (LH) COVID-19 by a patient [31], the features of which have been identified in individuals irrespective of the initial illness severity [32]. One characteristic of LH COVID-19 is that the symptoms may either persist past the 3–4 week mark and/or new symptoms may develop after the 3–4 week mark. In fact, the National Institute for Health and Care Excellence has defined the LH or post-COVID-19 syndrome as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks (3 months) and are not explained by an alternative diagnosis” [33]. LH COVID-19 appears in the literature under several synonyms: post-COVID-19 condition (WHO defined), post-acute COVID-19 syndrome (PACS) [34] and post-acute sequelae of COVID-19 [32].

Neurological symptoms discussed above may contribute individually or synergistically to the persistence of neurological pathophysiology past the acute phase. The loss of BBB integrity and neuroinflammation [35–37], coupled with coagulopathy and the development of micro-emboli in the CNS [38, 39] may lead to the progression

of LH COVID-19. Additionally, factors associated with hospital stay (i.e. intubation, mechanical ventilation and the use of sedatives) may further exacerbate the clinical course in those with severe acute symptoms. Neuro-psychiatric features of LH COVID-19 are likely related to prolonged stress associated with the pandemic and loss of family members/friends [40].

A recently published meta-analysis aimed to evaluate the neurological and neuropsychiatric features of LH COVID-19 in three cohorts: outpatient (community), non-ICU hospitalized an ICU hospitalized and at two different time points: 3–6 months and past the 6 month mark after the initial infection [41]. Primary outcomes included neurologic and psychiatric symptoms. Neurologic symptoms included: anosmia, dysgeusia, headache, cognitive dysfunction, fatigue, chronic fatigue syndrome, post exertional malaise, pain, peripheral nervous system symptoms. Neuropsychological symptoms included: anxiety, depression, sleep disturbances and/or insomnia and PTSD. A total number of full text articles screened were 80, and 18 studies, including 10,530 patients met the inclusion criteria. The most frequent neurological symptom of LH COVID-19 was fatigue (37%), followed by brain fog (32%), sleep disturbances (31%) and memory issues (28%). The prevalence of these symptoms tended to be higher in non-hospitalized individuals. Similarly, the neuropsychiatric symptoms of anxiety (31%) and depression (27%) were higher in the community cohort compared to the hospitalized patients (6% and 12%, respectively). Additionally, the neuropsychiatric symptoms substantially increased from mid-term follow-up to long term follow-up (i.e. past 6 months), suggesting that LH COVID-19 patients may experience increasing neuropsychiatric burden well past the initial infection. It is however not known when and whether it tapers off. On the other hand, the neurological symptoms in this cohort appear to progress from mid- to long-term highlighting that this may be the critical period of LH COVID-19 during which patients should be screen for neurological pathophysiological events and represents the critical therapeutic window. Other large retrospective cohort studies reported similar timelines [40, 42]. This may be explained by the chronic aspect of neuro-inflammation that ensues secondary to initial infection, leading to neuronal loss in that critical time period.

Taken together, the existing large cohort studies [40, 42] and meta-analyses [41] indicate that neurological and neuropsychiatric symptoms are a common feature of LH COVID-19, with specific symptoms occurring in as much as a third of the individuals who were infected with SARS-CoV2. Future research should be directed towards identifying the therapeutic strategies during the critical window, which appears to be 3–6 months post-acute illness, in an effort to decrease neuroinflammation, restore the blood brain barrier and prevent neuronal loss.

3. Chronic stress associated with COVID-19: multifaceted attack on the cardiovascular system

The cardiovascular system is one of the direct targets of SARS-CoV2 made possible by the viral entry into the cells via ACE2 receptors expressed on endothelial cells and cardiomyocytes. The myocardial injury associated with the acute COVID-19 illness has been well documented [43–46]. The responsible mechanisms include direct cytotoxicity [47] and/or dysregulation of the renin angiotensin system (RAS) [33] and the immune response [33, 34]. The initial insights into myocardial injury came from autopsy studies which reported the presence of SARS-CoV2 pools located not in the cardiomyocytes but rather in interstitial cells and resident macrophages [48].

Perseverance of these viral reservoirs is still debatable and potentially insidious as they could play an important role in myocardial and vascular sequel in LH COVID-19. Furthermore, psychological or mental stress-related consequences of the COVID-19 pandemic are expected to contribute to the rising cases of cardiovascular disease. The link between mental stress and coronary artery disease, atrial fibrillation and stroke has been reported in various studies [49–52]. A large multicenter, multinational study, INTERHEART, reported after adjustment for covariates a more than 2-fold increase in the risk of myocardial infarction as a consequence of mental stress [53]. Although the long-term implications of COVID-19 pandemic on cardiovascular health are yet to be realized, previous work done in this area foreshadows a significant uptick of CVD globally, and independently of other comorbidities.

3.1 Chronic stress-associated effects on the central nervous and the cardiovascular systems

In order to study stress as a risk factor, a proper definition must be set in place. The first distinction that must be made is between the stressor and the response of an individual to that stressor (i.e. how well they can cope with it). A stressor is not necessarily perilous *per se*, neither physiologically or psychologically, as there are many stressors that contribute to desirable outcomes. Much like physical exercise represents a stressor that leads to improved cardiovascular and musculoskeletal health, some psychological stress increases readiness and attention resulting in better outcomes in scholarly activities or sporting competitions. It is when individuals have unique perceptions of the stress and their inability to cope with it that creates a favorable milieu for psychological disturbance and new onset CVD. In fact, different personality types have been reported to be more susceptible to CVD as a consequence of mental stress, including Type A (hostile and angry outlook) [54] and Type D (tendency for pessimism and social inhibition) personalities [55]. Given that the COVID-19 pandemic has brought groups of stressors globally, the impact on psychological and cardiovascular well-being remains to be described.

The CMS rodent model is perhaps the most used in studying mental stress that humans endure and has the highest constructive, face and predicative validity [56]. It consists of exposing the animals to a series of mild, yet unpredictable stressors for at least 4 weeks. One could argue that this is a high-fidelity model of the pattern of stressful events that people experienced consistently during the COVID-19 pandemic, and in that view the data generated in CMS rats may necessitate a closer examination in terms of the CVD comorbidities after the chronic stress to inform future treatment strategies. Namely, the data has shown that rodents exposed to CMS develop depressive-like symptoms and behaviors with adverse cardiovascular symptoms including reduced heart rate variability, elevated resting heart rate, reduced baroreceptor function and increased sympathetic nervous system activity [6–8, 57]. The sympathetic drive has been shown to be mediated at least in part by the paraventricular nucleus (PVN), and via the vasopressinergic system rather than oxytocin [7, 8]. The CMS rats have also been shown to have increased expression of vasopressin receptors V1a and V1b in the PVN and that the simultaneous inhibition of both V1a and V1b receptors produced maximal inhibition of the neurocardiovascular responses to the exogenous vasopressin administration [7].

Stress can be categorized as acute, lasting seconds to weeks, and chronic, in the months to years range. COVID-19 pandemic-associated stress thus falls into the latter category, and further can be described as CMS. Chronic stressors associated with

work and life related issues, such as injustice, effort-reward imbalance, marital stress at home, lack of life partnership, financial stress have all been shown to increase the risk of CVD [58–61]. Studies in humans have relied on measuring several parameters of the cardiovascular system function to assess the impact of mental stress, including cardiovascular reactivity, levels of catecholamines and inflammatory markers, heart and brain imaging, Holter monitoring and measures of endothelial function with flow-mediated dilatation [62–65]. It has been suggested that it is not the cardiac function but rather the vasculature, endothelium in particular, where the mental stress translates into CVD. Studies done in monkeys where they were exposed to a novel social environment showed increased endothelial damage in the thoracic aorta and coronary arteries [66]. Other studies in mice reported that both acute and chronic stress reduce the expression of nitric oxide synthase [67, 68], which is responsible for the synthesis of the vasodilatory molecule nitric oxide, leading to endothelial dysfunction. Stimulation of the sympathetic nervous system further increases local norepinephrine production and increase in the expression of adhesion molecules on the endothelium, and cytokine and chemokine production by macrophages and vascular smooth muscle cells. These feed forward cycles ultimately lead to leukocyte adhesion, vascular inflammation, atherosclerotic plaques instability, precipitating a cardiovascular event. Therefore, it is apparent that CMS endured during COVID-19 pandemic may cause similar vascular and endothelial dysfunction in humans as was shown in the above-described animal CMS models.

Chronic mild stress that individuals worldwide have endured during the COVID-19 pandemic has put them at a higher risk of developing anxiety and depression [69]. Lockdown policies instituted across the world resulted in isolation from human contact, worsening dementia and anxiety in individuals in long-term care facilities, exacerbation of conflict due to confinement and fear and confusion resulting from continuous bombardment with reporting information on all media, many of which were unreliable. Additionally, physical activity decreased partly due to the closure of fitness facilities as well as the lack of motivation and fear of SARS-CoV2 infection when leaving outside to obtain exercise. Some of the examples of reduced physical activity can be appreciated from the data from 30 million Fitbit activity tracker users, which showed a significant reduction in daily step counts by as much as 38% in Spain [70]. Similar data was obtained from analyzing step count trends from the app Argus in almost half a million users- a mean reduction in activity by 27.4% [71]. Some implied outcomes from these reductions in daily activity include exacerbation of hypertension. Several cross sectional studies indicated that reductions in step counts led to an increase of systolic blood pressure (SBP) of up to 7 mmHg [72, 73] and an increase of 4.5 mmHg for every additional hour of sitting every day [74]. Other behaviors during the pandemic that could have deleterious effects on blood pressure management include increase in body weight [75], increased sodium and decreased potassium intake [76, 77] which is particularly detrimental in the western countries where dietary intake of sodium is already high [78–81], and increase in alcohol consumption [82–84].

Most notably, CMS associated with the pandemic is expected to have adverse consequences on BP in both normotensive and hypertensive individuals. Although no study to date has reported direct associations related to COVID-19, published data indicate that chronic stress leads to an increase in the sympathetic drive as assessed with norepinephrine levels, changes in heart rate as well as via direct neurography [85–88]. Published clinical evidence repeatedly shows that depressed patients are at a higher risk of developing CVD which persists for a decade following the initial onset of depression [89–91]. This relationship is not unipolar, as patients with CVD have been

shown to develop depressive symptoms [90–93]. Some of the mechanisms explaining the co-occurrence of depression and CVD include neuroinflammation [94] and autonomic dysfunction [95], but they are by no means an exhaustive list (**Figure 1**).

Important knowledge has been gleaned from reliable, validated rodent models of CMS [96], which are still utilized to tease apart the mechanistic links between CVD and stress/depression. Importantly, the new and ongoing investigations have been focusing on explaining the difference in vulnerability of individual animals to stress-associated CVD development [97–100], much like occurs in humans. Rodents exhibit two distinct coping styles when exposed to stress: [1] the proactive coping, which is characterized by more offensive, aggressive and impulsive behavior; and [2] and reactive coping, which is characterized by more cautious and fearful behavior [99, 101]. In addition to the behavioral differences, physiologically the two differ as well, where the proactive (active) copers exhibit heightened sympathetic activity and low HPA axis reactivity and the reactive (passive) copers show the opposite trends [99, 102]. The passive coping rats were also shown to have persistently elevated levels of pro-inflammatory cytokine IL-1β and oxidative stress [103], and it is thus plausible that neuroinflammation is at the intersection of depressive symptoms and CVD.

The sex-based dichotomy in the prevalence and severity of depression has been well-characterized [104, 105]. Furthermore, the efficacy of antidepressant pharmacotherapeutic agents also differs between men and women [106, 107]. Likewise, women are more likely to develop CVD that co-occurs with depression [108]. A growing body of evidence has emerged indicating that COVID-19 pandemic has increased the incidence of depression, with the meta-analysis of 12 community-based studies worldwide highlighting a prevalence of depression of 25% [109], with female gender emerging as a significant risk factor [110–112]. One study reported that women under 50 persist more devastating symptoms such as fatigue, myalgia, brain fog and fatigue after being hospitalized for COVID-19 [113]. Animal model studies of CMS that address this disparity in males and females are scarce, and some have shown differences in behavioral and hormonal profiles. Anhedonia associated with depressive-like state in CMS rodents is typically measured by an intake of 1–2% sucrose solution, and has been found to be more pronounced in females than in males [114]. The same study found no differences in the corticosterone levels however, indicating similar stress hormonal profiles. These findings are the extend of our understanding of sex-based differences in CVD susceptibility as a function of chronic stress thus representing a large gap in knowledge that future preclinical studies should address. Developing treatments that will target both the depressive symptomatology and the cardiovascular pathology, while also being titratable, will be of utmost importance since there may be a difference in the magnitude of effects caused by chronic stress associated with the pandemic between women than men.

3.2 Long haul COVID-19: emerging effects on the brain, heart and vasculature

During the acute phase of SARS-CoV2 infection, the viral entry into the CNS can be accomplished either directly or indirectly (via neuroinflammation) [115]. The direct viral entry, as mentioned previously, can occur via the olfactory [116] or terminal cranial nerves [117]. ACE2 expression has been recognized on endothelial cells, pericytes and astrocytes, allowing the viral invasion of the CNS via compromised BBB. Alternatively or even additionally, the virus could traverse the microvascular endothelial cells, as has been shown [118]. Consequently, the BBB leakage would allow the influx of the circulating pro-inflammatory cytokines, chemokines and

mediators, further perpetuating neuroinflammation. *In vitro* studies also described the capabilities of SARS-CoV2 to initiate activation of astrocytes and microglia via its structural protein subunit (S1) [119]. This has been confirmed in autopsy studies of COVID-19 patients showing enlarged astrocytes and activated microglia [37]. Under normal physiological conditions, astrocytes play a crucial role in neurotransmission, as they control the synthesis of most essential neurotransmitters glutamate and GABA [120]. Additionally, astrocytes are involved in maintenance of synaptic plasticity via reuptake and recycling of neurotransmitters [121]. Under inflammatory conditions (i.e. SARS-CoV2 infection) astrocytes become reactive, which disrupts the glutamatergic balance, leading to excess extracellular glutamate contributing to dysfunction in both the CNS [58] and the cardiovascular systems [122]. Reactive astrocytosis is further supported by microglia via the NFkB pathway [123]. In the absence of the mechanisms that will shut down reactive astrocytosis (i.e. during COVID-19) the process could lead to the formation of astrocytic scars and in the long term neuronal death and neurodegeneration. Data describing the contribution of reactive astrocytosis in LH COVID-19 is lacking. One study so far has been published that measured plasma biomarkers of CNS injury in 100 COVID-19 survivors in Sweden. The biomarkers included nuerofilament light chain, glial fibrillary acidic protein (GFAP) and differentiation factor 15. In the acute phase, patients with severe symptoms had elevated neurfilament light chain compared to both age-matched controls and mild and moderate COVID-19, as well as higher GFAP than controls. However, after the median follow up of 225 days all CNS injury markers normalized and were indistinguishable from those found in healthy controls [124]. Since emerging data are pointing towards increased neuropathological manifestations one-year out compared to 6 months out [7], more studies are urgently needed to explain the mechanistic details and thus inform appropriate therapeutic strategies.

Data from the prospective post-acute follow up studies focusing on cardiac events have been more abundant in the literature compared to those on the CNS abnormalities. Several large (n > 400) observational studies are still ongoing in 2022. Transthoracic echocardiography and cardiac magnetic resonance are the gold standard techniques used in the diagnosis of cardiac pathologies [125, 126]. The vast majority of the studies have reported the presence of pericarditis, right ventricular dysfunction and myocardial infarctions [127–133]. Persistent myocarditis was reported in a cohort of 100 patients [127], while in another study of healthcare workers matched for comorbidities and severity of infection showed no difference in cardiac abnormalities 6 months post-infection [128]. Studies in athletes [129–132] were undertaken within 1–2 months of infection, and the prevalence of myocarditis is generally considered to be low (0–3%), albeit studies beyond the 2 month mark are lacking. Echocardiographic studies have consistently reported right heart abnormalities [133–135] while the left systolic function is significantly less impaired [133, 136], even in patients with severe acute symptomatology. On the other hand, perhaps the emerging trend that will have to be closely monitored in LH COVID-19 is the diastolic dysfunction, as it was shown to be common in up to 60% of hospitalized patients [137]. It is thus plausible to speculate that the pathologic changes in diastology could manifest during LH COVID-19, given the time lapse from the initial infection. In terms of vasculature, one angiography study reported an association between vascular inflammation caused by the variant B1.1.7 (WHO label Alpha) and increased mortality risk [138]. Although multiple studies have been published so far that have highlighted or implied the development of cardiovascular pathologies in LH COVID-19, one common denominator of limitations in most of them is that the comparator

groups were either healthy individuals or individuals unmatched for comorbidities. Perhaps the most important consideration should be the lack of pre-COVID cardiac imaging studies, which makes it difficult to discern whether the pathologies observed were due to COVID-19 or other comorbidities, or perhaps both. Nevertheless, given the non-invasive nature of echocardiography, it likely behooves the cardiac clinicians to implement cardiac imaging in LH COVID-19 given the evidence from prospective studies and the available therapeutics for ensuing cardiac pathologies.

The concerning aspect of the known and implied consequences of COVID-19 discussed above and LH COVID-19 is that these pathological processes do not exist in isolation and ultimately lead to multisystem dysfunction. A multi-organ magnetic resonance imaging study on a small cohort of recovered COVID-19 patients and matched controls revealed some level of abnormalities in the lung (60%), heart (26%), liver (10%), kidneys (29%) and brain (11%) [18]. Recovery from multisystem damage has been shown to be impeded by the persistent pro-inflammatory state [139] as well as endothelial dysfunction [140–142] and perpetual prothrombotic state [143]. These studies highlight the importance of approaching treatment strategies from the multisystem perspective rather than treating isolated pathologies. For example, anti-thrombotic therapy may be beneficial for individuals who present with the prothrombotic phenotype and have persistent inflammation in their LH COVID-19 phase.

4. Conclusions

According to the above discussed evidence and implications, the potential neurologic and cardiovascular consequences (**Figure 1**), coupled with the ensuing healthcare burden of COVID-19 necessitate a careful crafting of the clinical approach in the coming months and years. Both individuals who survived the infection and those who survived the pandemic without becoming infected with SARS-CoV2 (but were exposed to CMS) are at an appreciable risk of developing neurogenic and neuropsychiatric disturbances (**Figure 1**), and thus mental health checks for virtually all individuals on an ongoing basis are warranted. Furthermore, female gender may add another layer of risk for developing depression and CVD as a consequence of pandemic-associated CMS exposure. Studies conducted so far underscore the utility of echocardiography in revealing COVID-19-associated pericarditis, myocarditis and right heart dysfunction. Furthermore, resolution of inflammation should be at the forefront of treatment strategies, since prolonged inflammatory state is associated with poorer outcomes and LH COVID-19 symptomatology. Ultimately, clinical vigilance in monitoring individuals' mental and cardiovascular health will be of utmost importance in the post-pandemic years and research strategies aimed at mitigating the defunct mechanisms at the intersection of neurological and cardiovascular pathologies are merited.

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