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Hyper/neuroinflammation in COVID-19 and suicide etiopathogenesis: Hypothesis for a nefarious collision?

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ABSTRACT

Accumulating scientific and clinical evidence highlighted pathological hyperinflammation as a cardinal feature of SARS-CoV-2 infection and acute COVID-19 disease. With the emergence of long COVID-19 syndrome, several chronic health consequences, including neuropsychiatric sequelae, have gained attention from the public and medical communities. Since inflammatory mediators have also been accredited as putative biomarkers of suicidal ideations and behaviors, hyper- and neuroinflammation might share some colliding points, overlapping and being interconnected in the context of COVID-19. This review aims to provide a summary of current knowledge on the molecular and cellular mechanisms of COVID-19-associated hyper/neuroinflammation with focus on their relevance to the inflammatory hypothesis of suicide development. Subsequently, strategies to alleviate COVID-19 hyper/neuroinflammation by immunomodulatory agents (many of which at experimental stages) as well as psychopharmacologic/psychotherapeutic approaches are also mentioned. While suicide risk in COVID-19 survivors - until now little known - needs further analysis through longitudinal studies, current observations and mechanistic postulates warrant additional attention to this possibly emerging mental health concern.

1. Introduction

From an outbreak of pneumonia-like respiratory illnesses in Wuhan, China at the end of 2019, the SARS-CoV-2 (COVID-19) has rapidly become a pandemic of immense public health concern. By early September 2021, more than 220 million people had been diagnosed with SARS-CoV-2 infection and more than 4.5 million people have succumbed to this infection (World Health Organization, 2021). Due to the rapidly mutating and highly infectious nature of COVID-19, most global public health initiatives focused their efforts on an accelerated development of preventative measures, diagnostic methods, and novel treatments. In this regard, several strategies, including vaccination, have been researched and refined for the prevention, detection, and control of COVID-19 (Majumder and Minko, 2021).

Besides these remarkable medical breakthroughs, a growing body of scientific literature has detailed several emerging COVID-19-related psychiatric complications, including increased suicide risk (Fiorillo and Gorwood, 2020; Vindegaard and Benros, 2020). In this context, a possible increase in suicide risk during the early stages of the pandemic had been predicted by the scientific community, due to the contribution

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of various interacting psychosocial factors (e.g., isolation, entrapment, substance abuse, financial stressors) and pre-existing psychiatric illnesses such as depression and history of suicidal crisis (Gunnell et al., 2020; Niederkrotenthaler et al., 2020; Reger et al., 2020; Sher, 2020a; Amerio et al., 2020; Costanza et al., 2020a). During the first wave of COVID-19, worldwide case reports and observational studies from psychiatric emergency departments documented an increase in suicidal ideation (SI) and behavior (SB) (Aly et al., 2020; Berardelli et al., 2020; Goyal et al., 2020; Liu et al., 2020; Mamun and Griffiths, 2020; Pirnia et al., 2020; Thakur and Jain, 2020; Ambrosetti et al., 2021a; Boldrini et al., 2021; Montalbani et al., 2021). However, these early findings could not be substantiated in more recent systematic reviews, meta-analyses, and time-series analyses (John et al., 2020; Kahil et al., 2021; Leske et al., 2021; Phiri et al., 2021; Pirkis et al., 2021). Compared to the pre-pandemic situation, only one meta-analysis reported increased SI and SB during the first pandemic's wave (Dube et al., 2021). On the contrary, the general population was more vulnerable to SI and SB development during later stages of the pandemic (Balestrieri et al., 2021; McIntyre et al., 2021). A possible explanation for this phenomenon may be the persistent and long-lasting impact of various psychosocial factors (Zortea et al., 2020), including the evolution of the global economic crisis (Sher, 2020b; Ambrosetti et al., 2021b; Costanza et al., 2021a; Pompili, 2021). Besides, the increase in suicide risk during the later stages of the pandemic might result from direct chronic biological consequences of the infection, including its hallmark pathology of hyperinflammation (Sher, 2021), defined as the rapid proliferation of effector immune cell subsets and the excessive production of a multitude of pro-inflammatory cytokines by both immune and parenchymal cells.

Given the emerging implications of systemic and neuroinflammatory processes in the development of SI and SB (Sher, 2021) and recent evidence of mental health deterioration in subjects with long COVID-19 syndrome (Brundin et al., 2017), it is possible that an elevated suicide risk might exist in COVID-19 survivors (Sher, 2020b, 2021). In light of this perspective, this review aims to highlight the current knowledge on COVID-19 associated-hyperinflammation and its possible involvement in SI/SB development.

2. Cellular mediators of COVID-19 associated hyperinflammation

A cardinal feature of SARS-CoV2 infection is the presence of a systemic inflammatory milieu called cytokine storm, including IL1, IL6, IL12, IL18, CCL2, CCL5, GM-CSF, TNF*a*, and IFNγ, storm (Arunachalam et al., 2020; Garcia-Beltran et al., 2021; Hadjadj et al., 2020; Lucas et al., 2020). Since ACE2, the cellular entry receptor of SARS-CoV2, is widely expressed in various tissues, including the brain, direct infection of vulnerable parenchymal cell subsets by SARS-CoV2 could result in dysregulated peripheral tissue inflammation as well as neurological complications in COVID-19 patients (Bridges et al., 2021; Chen, Wu et al., 2020; Hensley et al., 2021; Ngo et al., 2021; Ziegler et al., 2020). While the hyperinflammatory syndrome in SARS-CoV2 infection is contributed by various effector cell types, emerging evidence has pointed to a critical participation of major innate immune cell subsets of both peripheral and CNS origins in this pathology.

2.1. Monophagocytes

The monophagocyte system consists of several subsets of circulating monocytes and tissue macrophages (Hussell and Bell, 2014; Kapellos et al., 2019; Ziegler-Heitbrock et al., 2010). In the context of SARS-CoV2 infection, the presence of ACE2 on monocytes and macrophages render them susceptible to this respiratory pathogen in both animal models and clinical specimens (Abassi et al., 2020; Bao et al., 2020; Zhao et al., 2020). The contribution of these cells to pathological inflammation observed in COVID-19 patients have been suggested by several important clinical observations that emerged during the early phase of the pandemic. First, patients with severe COVID-19 disease are characterized by elevation of circulating inflammatory markers such as IL1, IL6, IL8, TNFα, all of which are chiefly derived from monocytes and macrophages (Huang et al., 2020). Second, the increased susceptibility of males to severe COVID-19 development is correlated high levels of innate immune cytokines such as IL8 and IL18 (Takahashi et al., 2020). Third, a multisystem inflammatory syndrome has been documented in pediatric COVID-19 patients, which shares striking clinical presentation with Kawasaki disease and macrophage activation syndrome (Dufort et al., 2020; Feldstein et al., 2020). Lastly, post-mortem histopathological analysis of COVID-19 patients revealed the presence of monophagocyte infiltrate and inflammatory activation in a multisystem manner (Bryce et al., 2021; Carsana et al., 2020; Fox et al., 2020; Gustine and Jones, 2021). Altogether, these findings suggest a pivotal involvement of aberrant activation of the monophagocyte system in COVID-19 hyperinflammatory syndrome.

Following these findings, mechanistic studies have attempted to delineate the relative contribution of circulating monocytes and tissue macrophages to the hyperinflammatory state in COVID-19 (Giamarellos-Bourboulis et al., 2020; Grant et al., 2021; Schulte-Schrepping et al., 2020; Szabo et al., 2021; Zhou et al., 2020). High resolution single cell analysis of the bronchial alveolar lavage fluid from COVID-19 patients demonstrated that lung macrophages resemble a subset of monocytes in the blood, prompting the possibility of sequential recruitment and in situ differentiation of these circulating precursor cells (Liao et al., 2020; Sánchez-Cerrillo et al., 2020). Furthermore, the bronchial alveolar lavage fluid samples from severe COVID-19 patients are also enriched for the monocyte chemoattractants, CCL2 and CCL7 (Zhou, Ren et al., 2020), suggesting that these might play an instrumental role in the recruitment of circulating inflammatory monocytes to the lung of patients with severe illness (Fig. 1A).

2.2. Mast cells

Mast cells are long-lived innate immune cells that not only provide the first line of host defense against viral and bacterial infections but also participate in the pathogenesis of allergic inflammation and neurological disorders (Georgin-Lavialle, Moura et al., 2016; Hendrikus et al., 2017). Emerging evidence has pointed to an involvement of mast cells in inflammatory syndrome associated with COVID-19 (Tan et al., 2021; Conti et al., 2020). Mast-cell-enriched mediators, such as carboxypetidase A3, chymase, tryptase, and serotonin, were elevated in sera of SARS-CoV2 infected patients and positively correlated with hyperinflammatory markers (Soria-Castro et al., 2021; Gebremeskel et al., 2021). In lung tissues of COVID-19 patients, post-mortem analysis revealed extensive presence of CD117 + mast cells that colocalized with IL1 and TNF*a* (Ribeiro Dos Santos Miggiolaro et al., 2020). Interestingly, this mast cell activation signature was absent in tissue samples from patients with H1N1 infection as well as health control subjects, highlighting the potential unique involvement of mast cells in COVID-19 (Motta Junior et al., 2020). Several mechanisms by which these cells become activated have been proposed (Gebremeskel et al., 2021; Motta Junior et al., 2020). Notably, a major mast cell-derived mediator, histamine, might play a pivotal role in the initiation of cytokine storm syndrome in COVID-19 patients due to its ability to trigger production of IL1 IL6, IL8, and several other inflammatory chemokines/cytokines (Motta Junior et al., 2020) (Fig. 1B). Last but not least, mast cell activation syndrome (MCAS) has been considered as a potential risk factor for the development of severe SARS-CoV2 infection as its prevalence closely corresponds to the estimated frequency of severe COVID-19 (Frieri, 2015; Molderings et al., 2010; Afrin et al., 2020). This multisystem syndrome is known to escalate shortly after exposure to an immunological stressor, such as infection or allergen, and therefore might represent an important driver of hyperinflammation in COVID-19 patients (Kempuraj et al., 2020a, 2020b; Romero-Sánchez et al., 2020).

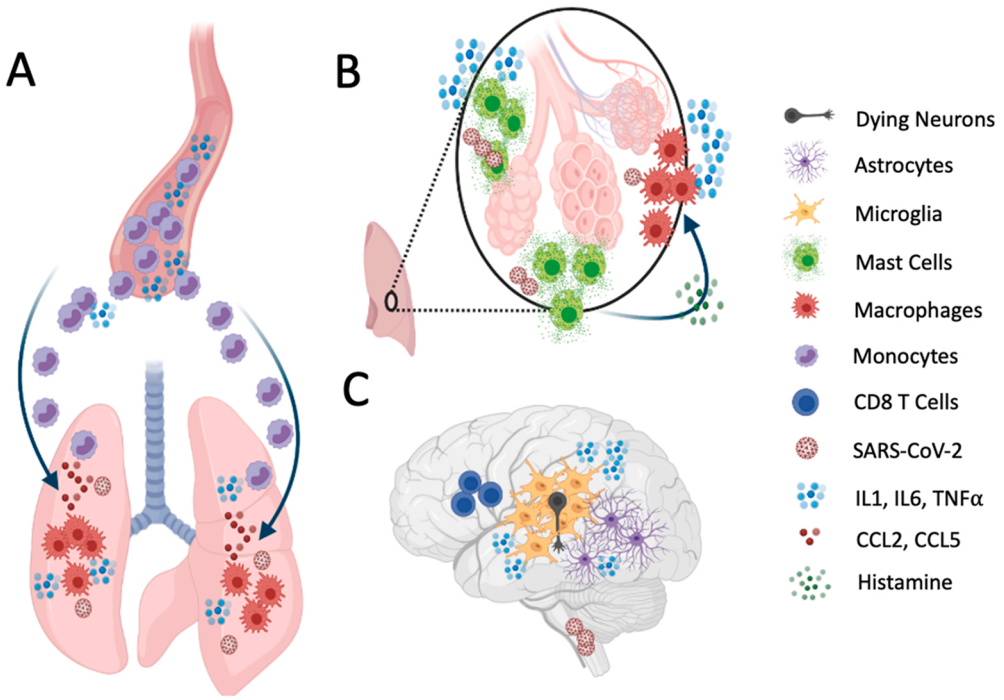

Fig. 1. Cellular mechanisms of COVID-19 hyperinflammation. *A. SARS-CoV2-activated aveolar macrophages produce both inflammatory mediators, such as IL1, IL6, and TNFα, and chemotactic molecules, such a CCL2/CCL5 to recruit circulating blood monocytes to the airways, amplifying respiratory hyperinflammation. B. SARS-CoV2-activated mast cells orchestrate airway hyperinflammation by secreting inflammatory cytokines and activating of aveolar macrophages* via *their production of histamines. C. Upon neuroinvasion of SARS-CoV2, dying neurons are surrounded by activated microglia, which serve as the communicating hub to sustain neuroinflammation by their production of inflammatory mediators and subsequent activation of astrocytes and CD8 + T cells.*

2.3. Glial cells

Microglia have been considered a central regulator of neuroinflammation via their production of various neurotoxic and inflammatory mediators such as IL1, IL6, and TNF*α* (Ajami et al., 2007; Ginhoux et al., 2010). Besides microglia, astrocytes are another major cell type that contribute to inflammatory reactions in the CNS (Linnerbauer et al., 2020). The earliest studies of neurotropic impact of SARS-CoV2 infection have documented meningoencephalitis and brainstem/olfactory bulb dysfunctions in COVID-19 patients, suggesting the presence of neuroinflammatory processes (Manganelli et al., 2020; Whitcroft and Hummel, 2020; Mondal et al., 2021; Yang et al., 2021). Transcriptomic analysis of cellular repertoire in the choroid plexus and cortices of COVID-19 patients also revealed marked perturbations in pathways associated with inflammation and viral entry at this CNS barrier (Pellegrini et al., 2020). In the brain parenchyma, several post-mortem histological studies revealed intense microgliosis nodules in various brain regions and perivascular spaces in majority of COVID-19 patients (Matschke et al., 2020; Schurink et al., 2020; Lee et al., 2021; Schwabenland et al., 2021). Notably, microgliosis was accompanied by their expression of various markers of inflammation (IL-1, IL-6, HLA-DR), suggesting an activated phenotype of these resident CNS immune cells (Matschke et al., 2020; Boroujeni et al., 2021; Lee et al., 2021; Poloni et al., 2021). These activated microglia were found to be in contact with astrocytes, CD8 + cytotoxic T lymphocytes, or surrounding dying neurons (neuronophagia), suggesting that these CNS innate immune cells are the communicating hub that orchestrates neuroinflammation (Fig. 1C). Astrocyte reactivity was also present in COVID-19 patients as evidenced by both histological and serological findings. this regard, astrogliosis was detected in the brain samples of COVID-19 patients (Matschke et al., 2020; Lee et al., 2021; Reichard et al., 2020). Similarly, a serum indicator of astrogliosis, S100b, was also elevated in moderate to severe COVID-19 patients and positively correlates with markers of inflammation (Aceti et al., 2020; Kanberg et al., 2021). Altogether, these findings highlight the central roles of these glial cell population in the initiation and propagation of inflammatory processes associated with SARS-CoV2 neuroinvasion.

3. Hyperinflammation as an etiological contributor to increased suicide risk in COVID-19?

Besides the immediate impact on COVID-19 pathology, immune-mediated hyperinflammation might also exert long-term health consequences on COVID-19 survivors. In fact, chronic comorbidities of virally infected survivors have been observed in previous pandemics and are particularly relevant for subjects experiencing long COVID-19 syndrome (Chacko et al., 2020; Rogers et al., 2020; Troyer et al., 2020). Among these complications, conditions of psychiatric nature, such as SI and SB are of immense public health concerns.

3.1. Inflammatory signature in suicide pathophysiology

As one of the most prominent causes of mortality in the world, suicide has a complex etiology that has been postulated to be the result of dynamic interplays between psychological stressors and neurobiological risks. Stressors from the environment (such as negative societal, familial and personal occurrences) and consequent hopelessness might constitute the triggering events for most suicidal acts while underlying neurobiological abnormalities might foster suicide vulnerability (Grunebaum et al., 2006; Aguglia et al., 2019b, Zortea, 2020, Aguglia et al., 2021a). While mood disorders, such as depression, have been frequently associated with increased suicide risk, several post-mortem studies and vivo studies of suicidal subjects have provided important insights on putative neurobiological origins of this psychiatric condition (Hawton and van Heeringen, 2009; Mann and Currier, 2010; Costanza et al., 2015; Turecki and Brent, 2016; Turecki et al., 2019; Costanza et al., 2020b). For instance, numerous biochemical and genetic indicators of suicide risks have been documented, including alterations in serotonergic, BNDF, and kynurenine signaling as well as other neurometabolic pathways (Sublette et al., 2011; Costanza et al., 2013; Aguglia et al., 2019a).

Besides these neurobiological factors, pathological inflammation has recently emerged as a potentially significant risk factor for SI/SB development and is of high relevance in the context of COVID-19 (Serafini et al., 2013; Black and Miller, 2015; Courtet et al., 2015; Miná et al., 2015; Ganança et al., 2016; Serafini et al., 2020; Aguglia et al.,

2021b). To date, most studies implicate inflammation, mediated by both soluble factors (IL1, IL6, and TNF*a*) and abnormally activated cell populations (monophagocytes and glial cells), in the pathophysiology of suicide (Fig. 2). In this regard, several studies have documented an association of various biomarkers of inflammation with suicide risk. Genetic analyses of suicidal subjects revealed an association between IL6, IL8, and TNF*a* and increased risk for suicidal attempts (SA) (Kim et al., 2013; Knowles et al., 2019). Additionally, IL6, TNF*a*, and CRP have been found to be abnormally elevated in sera samples of depressed suicide attempters (Aguglia et al., 2020). Corroborating findings from several metanalyses also demonstrated that subjects with active SI and past history of SA also exhibited higher circulating levels of IL1 and IL6 (Black and Miller, 2015; Ducasse et al., 2015). In the CNS microenvironment, IL6 was found to be elevated in the cerebrospinal fluid of suicide attempters and correlated with a history of violent suicidal acts and depression scores (Lindqvist et al., 2009). This inflammatory cytokine expression in the CSF also correlated with suicidal risk in patients with depressive symptoms (Bay-Richter et al., 2015). Consistent with these fluid biomarker studies, post-mortem analyses of brain samples from suicidal subjects showed that IL1, IL6, and TNF*a* were elevated in various regions of the prefrontal cortex, pointing to the possible involvement of neuroinflammation in SI/SB development (Pandey et al., 2018; Wang et al., 2018).

While some contradictory observations for the involvement of selected inflammatory mediators in SI/SB development warrant further confirmatory analyses (Kim et al., 2008; Gabbay et al., 2009; Grassi-Oliveira et al., 2012; Coryell et al., 2018), it's worth noting that these effector molecules are chiefly produced by peripheral innate immune cells and CNS glia, supporting the possible involvement of these cell types in this phenomenon (Baharikhoob and Kolla, 2020). In fact, a proinflammatory phenotype of circulating monocytes has been observed in blood samples of depressed suicidal subjects (Nowak et al., 2019). Elevated frequencies of blood monocytes and granulocytes have also been linked with increased suicide risk (Keaton et al., 2019). Similarly, macrophage infiltration into the brain parenchyma of depressed suicides has been noted by elevated expression of CD45, Iba1 as well as a classical macrophage chemoattractant, CCL2 (Torres-Platas et al., 2014). Astrocytic hypertrophy has also been observed in the anterior cingulate, thalamus, and caudate regions of depressed suicidal subjects. Furthermore, astrogliosis and microgliosis were observed in selected brain regions of suicide victims, suggesting widespread neuroinflammation might not be necessary to precipitate an increased risk for suicide (Schlicht et al., 2007; Steiner et al., 2008; Torres-Platas et al., 2011; Schnieder et al., 2014; Torres-Platas et al., 2014; Torres-Platas et al., 2015; Cabrera et al., 2019). One prominent hypothesis suggests that inflammatory milieu produced by CNS macrophages and glial cells might cause specific induction of serotonergic and glutamatergic neurotoxicity (Pompili et al., 2017; Suzuki et al., 2019). Alternatively, inflammatory mediators might directly induce neurotoxicity and/or excitotoxicity in vulnerable neuroanatomical circuits that have been implicated in SI/SB development.

3.2. *COVID-19 associated inflammation as a suicide risk factor?*

While long term analysis of suicide risk in COVID-19 patients is absent, emerging evidence has brought attention to the possible impact of COVID-19 on suicide risks of the infected. In fact, in a 6-month study of 40469 patients who were diagnosed with COVID-19 infection, 22.5% were presented with neuropsychiatric co-morbidities, including SI (Nalleballe et al., 2020). Another study of 16315 young adults diagnosed with COVID-19 in the US revealed a 13.4% rate of SI and 1.3% rate of SA, which are both positively correlated with disease severity (DeVylder et al., 2021). Notably, suicide risk might be elevated in infected subjects with a history of SI. As demonstrated in a study of US veterans, those who were infected with SARS-CoV2 were more likely to exhibit peri-pandemic SI, whose strongest independent predictive factors include the existence of this neuropsychiatric symptom before the pandemic (Na et al., 2021).

Recent studies have delineated the contribution of major innate immune cell subsets relevant to COVID-19 associated hyperinflammatory pathology to specific psychiatric risk factors of suicide (Fig. 2). In this regard, mast cell activation has been shown to be associated with depression (Moura et al., 2011; Moura et al., 2012; Georgin-Lavialle, Gaillard et al., 2016; Georgin-Lavialle, Moura et al., 2016), one of the strongest risk factors for suicide (Coughlin and Sher, 2013, CDC USA.gov 2020). Therefore, dysregulated mast cell activity as

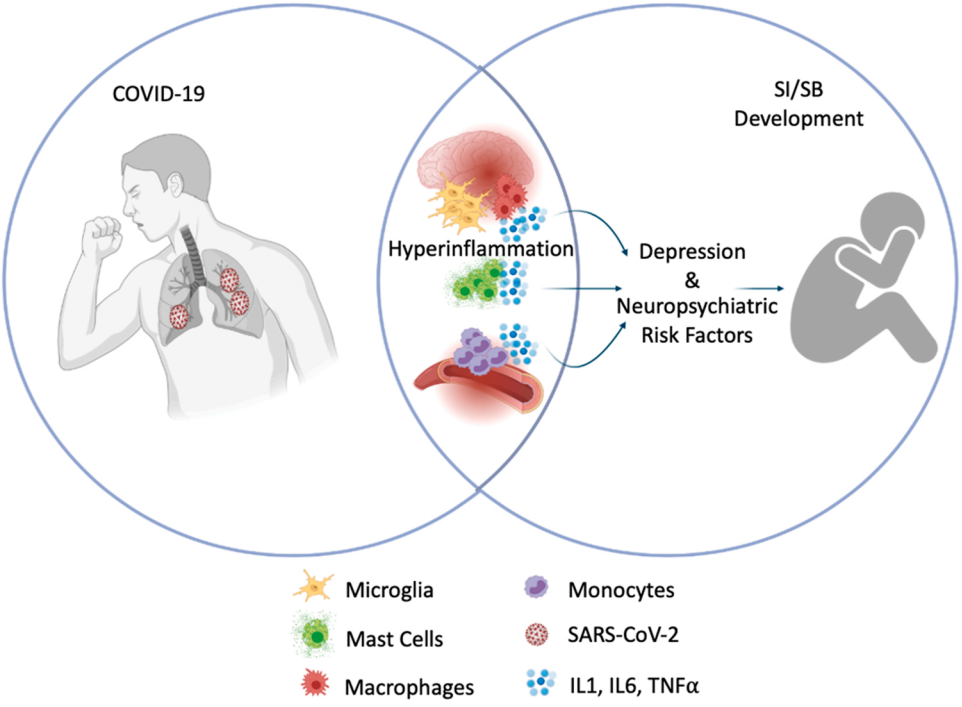

Fig. 2. Hyperinflammation as the possible colliding point between COVID-19 and SI/SB development. *Hyperinflammation in COVID-19 is characterized by activation of several immune cell types in the circulation/peripheral tissues (monocytes and mast cells) as well as in the central nervous system (microglia and macrophages). These inflammatory mediators have been linked to depression and other neuropsychiatric risk factors of SI/SB development, prompting the possible presence of hyperinflammation as the precipitating factor for increased suicide risk in COVID-19 survivors.*

a result of SARS-CoV2 infection might heighten the risk for depression-related SI/SB development. Other studies have also documented the presence of several neuroinflammation-associated comorbidities in COVID-19 patients, including stroke, headache, and depression, all of which are independently associated with increased suicide risk (Coughlin and Sher, 2013; Hudzik and Marek, 2014; Asadi-Pooya and Simani, 2020; Mazza et al., 2020; Steardo et al., 2020). Lastly, the overlapping presentation of psychosis and depression with peripheral monophagocyte activation as well as increased suicide vulnerability also suggests the possible existence of a common inflammatory pathway by which the monophagocyte system contributes to the development of this complex neuropsychiatric phenomenon (Maes et al., 1992; Bergink et al., 2014). Along with previous implications of the role of several soluble mediators (IL1, IL6, and TNFα) in both SI/SB development and COVID-19 hyperinflammation, these collective findings point to the possibility that COVID-19 survivors might be at a higher risk for this neuropsychiatric condition.

4. Inflammation as a therapeutic target in COVID-19 and its relevance to suicide prevention

4.1. Anti-inflammatory therapies for COVID-19

Several treatment modalities for COVID-19 have been developed to address major drivers of pathological inflammation in this disease. IL6 represents one of the most attractive therapeutic targets for COVID-19 as serum Ievels of this inflammatory cytokine have been shown to be a reliable biomarker for cytokine storm syndrome and disease severity (Chen et al., 2021; Leisman et al., 2021). A series of inhibitors of IL6 signaling, which is present in inflammatory monocytes and macrophages, are in various phases of clinical trials for severe COVID-19 patients (Alattar et al., 2020; Sciascia et al., 2020; Xu et al., 2020; Sieper et al., 2015; Eskandary et al., 2019; Meira et al., 2021). Trials to evaluate blockade of other inflammatory cytokines such as TNFα and IL1 are also in progress (Cavalli et al., 2020; Feldmann et al., 2020; Huet et al., 2020; Robinson et al., 2020). Chemokines which orchestrate the recruitment and accumulation of monophagocytes also represent an alternative class of inflammatory targets for COVID-19 patients (Zhao, 2010; Patterson et al., 2020). Additionally, mast cell stabilizers or modulators of secreted inflammatory products from mast cells are attractive therapeutics for COVID-19 (Kazama, 2020; Hafezi et al., 2021; Wu et al., 2020; Zhou et al., 2015). These modulators of mast cell function have either been proposed for or currently in trials for COVID-19. On the other hand, treatments focusing on resolving neuroinflammation in COVID-19 have not yet been evaluated in the clinics. However, candidate inhibitors of microglial activation have been proposed to mitigate the impact of neuroinflammation-associated pathology in COVID-19 patients (Chaves Filho et al., 2021; Kempuraj et al., 2020a, 2020b).

While inhibitors of specific inflammatory pathways have shown both promising clinical results and/or provided novel mechanistic insights into their relative contribution to COVID-19 associated cytokine storm syndrome, other strategies to broadly suppress hyperinflammation have also been attempted, including JAK1/2 and BTK inhibitors (Cantini et al., 2020; Richardson et al., 2020; Convertino et al., 2020; Kaliamurthi et al., 2021; Stack et al., 2021). Additionally, clinically approved drugs that have been shown to be effective in suppressing systemic or tissue inflammation (particularly the respiratory tract), such as tacrolimus, sirolimus, prednisolone, and dexamethasone, are also under investigation (Moutsopoulos et al., 2018). Lastly, neuropsychiatric medications, including risperidone, paliperidone, olanzapine, aripiprazole, that possess dual anti-inflammatory and anti-psychotic properties, have been trialed in COVID-19 patients with high risk for psychiatric complications (Canal-Rivero et al., 2021; Crespo-Facorro et al., 2021; Tendilla-Beltrán and Flores, 2021).

4.2. Therapeutic considerations for anti-inflammatory treatments in suicide prevention

As discussed above, efforts to address inflammatory pathology in COVID-19 have provided promising results. However, whether or not suppressing inflammation could provide protection against SI/SB development and other psychiatric comorbidities remains to be investigated. Notably, a recent study has demonstrated the potential efficacy of anti-inflammatory medication in reducing risks of SI, providing the first proof of concept for targeting inflammatory pathways in suicide prevention (Lehrer and Rheinstein, 2019). However, some associations between suicide risk and anti-inflammatory therapies have been reported. In this regard, the controversial usage of the anti-malarial drug, hydroxychloroquine, in COVID-19 patients has been linked to significant cardiotoxicity and other neuropsychiatric complications, including suicide (Ahmadizar et al., 2020; Boulware et al., 2020; Cavalcanti et al., 2020; Hamm and Rosenthal, 2020; Ong et al., 2021). In light of this clinical experience, possible risk of suicide must be carefully examined for all anti-inflammatory therapies, in the context of suicide prevention for COVID-19 survivors.

Beside anti-inflammatory therapies, psychiatric assessment, which has been shown to be highly effective in suicide prevention, must also be provided to the survivors of COVID-19. Patient assessment for this suicide risk factor after COVID-19 recovery should be considered (Sher, 2020a). Such evaluation often requires consistent post COVID-19 follow-ups in the presence of an interdisciplinary team of neurologists, psychiatrists, and psychologists (Sher, 2020a). Special attention must be provided to COVID-19 patients with history of SI and SB, depression, psychotic disorders as well as emerging evidence of impulsivity, emotional lability, irritability, anger and apathy (Baertschi et al., 2019; Costantini et al., 2021; Costanza et al., 2021b). Information from these clinical assessments may help identify specific targets for both psychopharmacologic and psychotherapeutic interventions so that a comprehensive care program could be provided to COVID-19 survivors (Costanza et al., 2020a; Postolache et al., 2021). Furthermore, the interactive nature of these psychotherapeutic targets could also address the psychological needs for caregivers and family members of COVID-19 survivors. Lastly, psychotherapy has emerged as a novel modulator of immune-related health (Shields et al., 2020). In this regard, recent studies have demonstrated that cognitive behavioral interventions could suppress the elevated expression of various inflammatory markers in both somatic illnesses and psychiatric conditions (Nemirovsky et al., 2021; Diaz et al., 2021; Sundquist et al., 2021). The direct impact of psychosocial interventions on excessive immune activation provides another line of support for the use of this modality against COVID-19-associated hyperinflammation and its possible sequelae of increased suicide risk.

5. Conclusion

Hyperinflammation, a central orchestrator of SARS-CoV2 pathogenesis, is a possible contributing factor to the development of a wide range of chronic neuropsychiatric complications, including suicide, in COVID-19 survivors. While it remains unknow to which extent anti-inflammatory therapies might be efficacious in preventing the development of these conditions, these observations above suggest that an integrated and multidimensional research efforts should be implemented to address this emerging unmet medical need. In addition, both pharmacological and psychotherapeutic interventions should be promptly designed and evaluated in anticipation of a possible increase in suicide risk in COVID-19 survivors.

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Competing interest

KDN is the scientific founder of Tranquis Therapeutics, a biotechnology company that develops novel treatments for neuroinflammatory and neurodegenerative diseases. KDN also serves a scientific advisor for Tochikunda, biotechnology company that develops SARS-CoV-2 diagnostic devices. All other authors declare no conflict of interest.

Data Availability

Data will be made available on request.

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