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COVID-19 as a polymorphic inflammatory spectrum of diseases: a review with focus on the brain

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Review Article

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Abstract

There appear to be huge variations and aberrations in the reported data in COVID-19 2 years now into the pandemic. Conflicting data exist at almost every level and also in the reported epidemiological statistics across different regions. It is becoming clear that COVID-19 is a polymorphic inflammatory spectrum of diseases, and there is a wide range of inflammation-related pathology and symptoms in those infected with the virus. The host's inflammatory response to COVID-19 appears to be determined by genetics, age, immune status, health status and stage of disease. The interplay of these factors may decide the magnitude, duration, types of pathology, symptoms and prognosis in the spectrum of COVID-19 disorders, and whether neuropsychiatric disorders continue to be significant. Early and successful management of inflammation reduces morbidity and mortality in all stages of COVID-19.

Summations

- Accumulating data regarding COVID-19 show huge variations but inflammatory polymorphism may explain such variations in the data and the spectrum of COVID-19 diseases.
- Interplay of factors, such as genetics, age, time, immune status and health status, contributes to inflammatory polymorphism and decides the magnitude, duration, types of pathology, symptoms and prognosis in the spectrum of COVID-19 disorders.
- Significant neuropsychiatric disorders are present in acute, mid and long COVID.
- Appropriate management of the polymorphic inflammation in each of the acute, mid and chronic stages of COVID-19 infection is critical for recovery from COVID-19.

Considerations

- Well-designed clinical trials are required to confirm the efficacy and timing of various inflammation modulation measures, including biologics, NSAID, antihistamines, glucocorticoids, sigma receptor agonists and antagonists.
- The neurobiology of brain area hypometabolism reported in COVID-19 is unclear and its relationship to neuropsychiatric disorders both require further research.
- Specific preventive measures and treatment of neuropsychiatric symptoms in different stages of COVID-19 require further research.
- Identification of factors associated with the development of long COVID requires further research.

Introduction

At the beginning, COVID-19 was regarded as an acute infectious respiratory disease, similar to the SARS episode almost 20 years ago. The much higher infectivity, morbidity and mortality of COVID-19 than SARS was soon recognised. It is now clear that COVID-19 is not a simple acute respiratory infectious disease, but is a spectrum of diseases, exhibiting a high degree of polymorphism in symptoms, progression and sequalae. With the increasing number of patients reporting neurological symptoms, the SARS-CoV-2 virus is emerging as a new neuropathogen, responsible for a spectrum of neuropsychiatric disorders (Beghi *et al.*, 2022, 2022b; Montalvan *et al.*, 2020).

The huge variance in published COVID-19 data and statistics from various sources around the world illustrated the polymorphic nature of COVID-19 very well. For example, the reported percentage of infected patients ending up with severe respiratory crisis, and the percentage of asymptomatic patients testing positive both showed significant variation across populations. They ranged

from a low of a few percent to a high of almost 50% (He *et al*., 2020; Hu *et al*., 2020; Huang *et al*., 2020; Mizumoto *et al*., 2020; Shi *et al*., 2020; Tian *et al*., 2020; Wang *et al*., 2020; Sah *et al*., 2021; Zhang *et al*., 2021b). Accepting that there was sampling bias and methodological differences across populations, including differences in the availability of medical care, hospitalisation, vaccination and viral testing, infected individuals not detected or unaware of their infections, or not reporting their infection due to other reasons, the size of the variance and heterogeneity in the reported data is still astonishing.

Of the infected, some patients (as high as 19%, according to the Centers for Disease Control and Prevention (CDC) assessed on November 19, 2022), failed to recover completely, with the lingering symptoms now commonly named as 'Long COVID', which seemed to be unrelated to the severity of the acute COVID-19 infection (Asadi-Pooya *et al*., 2021; Crook *et al*., 2021; Fernández-de-Las-Peñas *et al*., 2021; Raveendran *et al*., 2021; Sykes *et al*., 2021; Yong, 2021; De Luca *et al*., 2022). A high proportion of long COVID symptoms appeared to be of a neuropsychiatric nature (Aiyegbusi *et al*., 2021; Taquet *et al*., 2021; Xie *et al*., 2022). Salamanna *et al*. (2021) reported that while 20.70% of long-term COVID-19 symptoms were related to abnormal lung function, neurologic complaints and olfactory dysfunctions exceeded it at around 24.13%, plus another 55.17% with symptoms such as chronic fatigue, headache and pain, all of which might be of neuropsychiatric origin. The prevalence of neuropsychiatric symptoms in long COVID was confirmed in the neuroepidemiology report of Beghi *et al*. (2022). Presence of neurological manifestations at all stages of COVID-19 was also found to be associated with a more severe disease, a higher death rate and the continued presence of long-term symptoms (Beghi *et al*., 2022b).

The terms acute, mid and long COVID are often used loosely to categorise three stages of COVID-19, with distinctive symptoms in each stage. In the F-18 Deoxy-glucose Positron Emission Tomography scanning technique (FDG-PET) studies of Kas *et al*. (2021) and Martini *et al*. (2022), the acute stage was regarded as within 1 month of infection, the mid stage is from after the acute stage to about 6 or 7 months and the late or long COVID stage is from after 6 months of infection. In terms of severity of infection, COVID-19 infection stages begin with the asymptomatic viral entry and replication, followed by viral dissemination with symptoms ranged from mild to moderate. Only some of those infected may progress into multi-system inflammation with severe symptoms and even end up in critical multi-organ dysfunction with endothelial damage and thrombosis (Cordon-Cardo *et al*., 2020). The two factors, temporal and severity of infection, in combination, appear to be useful in understanding the progress and polymorphic nature of COVID-19.

Infection by the SARS-CoV-2 virus alone appeared to be insufficient for development of the spectrum of COVID-19 diseases (Al-Aly *et al*., 2021; Michelen *et al*., 2021; Cohen *et al*., 2022). We discuss a hypothesis that COVID-19 inflammatory polymorphism is the basis underlying the spectrum of COVID-19 disease, determines the severity of symptoms, as well as the response to treatment. A substantial amount of new data has appeared in the literature since our last reviews on COVID-19 and neuroinflammatory disorders (Tang *et al*., 2017, 2021, 2022a; Leonard, 2018).

Method

We searched the English language literature, including foreign-language publications with informative abstracts in English, up to January 20th 2023, using PubMed (https://pubmed.ncbi.nlm.nih.gov), crossing the keywords 'COVID-19', 'long COVID', 'Kawasaki disease', 'SARS-CoV-2 virus', respectively, and in turn with the following words: brain, psychiatric disorders, depression, neurodegeneration, neuroinflammation, polymorphism, brain circuits, neurotransmitters, histamine, sigma receptor, cortisol, glucose metabolism, brain metabolism, immunological response, brain imaging and neurotransmitter imaging. We focused mainly on the polymorphism of COVID-19 inflammation, COVID-19-induced changes in brain area and neurocircuit functions, neurotransmitters and their receptors and brain metabolic changes. Manuscripts were included in this review only after all three authors evaluated the quality of the research and relevancy to the various sections of this review. Reviews of a general nature without data were excluded. Health statistics were obtained from the World Health Organization (WHO) and Centers for Disease Control and Prevention, USA (CDC) websites, accessed on 10th November 2022.

Results

Inflammation

Inflammation is a critical component in the progression of many diseases. For example, there is strong evidence that sustained and abnormal local microenvironmental immune response as well as systemic inflammation would lead to progression of tumours and many other diseases in human (Coussens & Werb, 2002; Diakos *et al*., 2014; Greten & Grivennikov, 2019; Singh *et al*., 2019). Some of the outcomes of patients in cancer and many other inflammatory-based diseases, including COVID-19, can be improved through appropriate management of the inflammation, which differs at different stages of the disease.

Inflammation in acute COVID-19

SARS-CoV-2 infects cells by binding their spike proteins to the angiotensin-converting enzyme II (ACE-2) receptors. Availability and quantity of ACE-2 receptors, genetically and epigenetically determined, is an important factor in the initiation and progress in COVID-19. The expression of ACE-2 receptors is linked to the immune and inflammatory response through a complex and not yet clear mechanism (Costagliola *et al*., 2021).

The high density of ACE-2 receptors in the olfactory epithelium explains the easy entry of the SARS-CoV-2 virus via this path (Bilinska *et al*., 2021; Butowt & von Bartheld, 2022; Mohamed *et al*., 2022). Thus, a common pathway for the virus to enter the human body is through the olfactory bulb to reach other parts of the body, including the nervous system. Temporary loss of smell, or anosmia, is now known to be one of the earliest signs of neurological damage in COVID-19. While anosmia is experienced by approximately 50% of those infected, inflammatory polymorphism is also seen, as anosmia in those infected varied tremendously between age categories, gender and individuals. Anosmia, more common in the elderly and in the female gender, may be an early sign of early neuro involvement in COVID-19 (Vallée, 2021). Anosmia, together with fatigue, headache, dyspnoea, are main long COVID-19 symptoms (Sudre *et al*., 2021). Lower expression of ACE-2 receptors in the female sex may explain the gender difference in incidence of anosmia observed. The ACE-2 receptor gene and other immunological genes are on the X chromosome, and oestrogen reduces the expression of ACE-2 receptors in females (Najafloo *et al*., 2021). With regard to age differences in anosmia, which is more common in the middle age group, nasal gene expression of ACE-2 was found to increase with age, reaching its highest level in middle age (Bunyavanich *et al*., 2020), until a decline occurs

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after degeneration of the whole olfactory structure in older age. Interleukin-6 (IL-6) has been reported to play a significant role in anosmia, with correlations between its levels and the time required for recovery (Cazzolla *et al.*, 2020). Genetic and epigenetic-based differences in inflammatory response may contribute to the variations in anosmia among those infected.

There are genetic and epigenetics factors reported in the expression of ACE-2 receptors (COVID-19 Host Genetics Initiative, 2021; Deng *et al.*, 2021; Ji *et al.*, 2022; Verma *et al.*, 2021; Yildirim *et al.*, 2021), which may explain the polymorphic nature of COVID-19 inflammation through the ACE-2 expression factor (Ragia & Manolopoulos, 2020; Secolin *et al.*, 2021; Severe COVID-19 GWAS Group, 2020). A number of HLA alleles and genes have been found to be associated with COVID-19 susceptibility and there are low-risk alleles as well (Fricke-Galindo & Falfán-Valencia, 2021). Epigenetic research suggested that other epigenetic changes, such as DNA methylation, ACE-2 gene methylation and post-translational histone modifications, may underline host, tissue, age and sex-based differences in the progress of viral infection (Chlamydas *et al.*, 2021).

Though the olfactory nerve is devoid of ACE-2 receptors, there are other explanations how the virus may enter brain areas via supporting cells and other adjacent cell types which do contain the ACE-2 receptors, such as the glial cells (Panariello *et al.*, 2020).

The sigma receptor and SARS-CoV-2 entry

The relationship between sigma receptors, psychiatric disorders and psychotropics was raised more than 20 years ago (Helmeste *et al.*, 1996a, 1996b, 1997; Tang *et al.*, 1997). However, its role in neurotransmission is still far from clear. The observation of possible reduced COVID-19 mortality in patients on certain psychotropics interestingly renews attention to this receptor (Tang *et al.*, 2021, 2022a). The accidental discovery of the benefit of fluvoxamine in COVID-19 can be explained by its sigma receptor affinity. Many more discussions regarding the beneficial role of antidepressant drugs in COVID-19 have appeared in the literature in the recent 2 years (Facente *et al.*, 2021; Hoertel, 2021; Hoertel *et al.*, 2021; Oskotsky *et al.*, 2021; Bonnet & Juckel, 2022; Borovcanin *et al.*, 2022; Firouzabadi *et al.*, 2022; Foletto *et al.*, 2022; Hashimoto *et al.*, 2022; Mahdi *et al.*, 2022; Nakhaee *et al.*, 2022).

After binding to the ACE-2 receptors, the SARS-CoV-2 virus interacts with the sigma-1 receptors located in the endoplasmic reticulum (ER), converting it into an ideal place for replication (Vela, 2020). Subsequent SARS-CoV-2 replication takes place in an ER-derived intermediate compartment in the ER-Golgi (Harrison *et al.*, 2020; Zhang *et al.*, 2020).

It has been suggested that ER stress due to the replication of the virus may lead to the development of a cytokine storm, with high mortality (Aoe, 2020; Banerjee *et al.*, 2020; Fajgenbaum & June, 2020; Harrison *et al.*, 2020; Santerre *et al.*, 2020; Zhang *et al.*, 2020). High levels of ER stress markers [i.e. glucose-regulated protein 78 (GRP78), C/EBP homologous protein (CHOP), phospho-extracellular signal regulated kinase (PERK)] in COVID-19 have been reported (Köseler *et al.*, 2020).

In addition, Sigma 1 receptors also regulate early steps of viral RNA replication (Friesland *et al.*, 2013). Downregulation of sigma-1 receptor expression may lead to a proportional decrease in susceptibility to virus infection in some individuals.

Thus, the polymorphic nature of the quantity and status of sigma receptors and ACE-2 receptors may contribute to the polymorphic nature of the inter-individual difference in susceptibility to the virus's infectivity.

Cytokines and cytokine storms

Cytokines are small signalling proteins and one of their functions is immunomodulation. Cytokines include interferons (IFN), interleukins (IL) and tumour necrosis factors (TNF). IFN are signalling proteins released in response to viral invasion or other foreign substances. Type 1 IFNs (such as IFN-α, IFN-β, IFN-ϵ, IFN-κ) are released by fibroblasts and monocytes. Release of IFN-α is inhibited by the cytokine IL-10. Type II IFNs (IFN-γ) are released by cytotoxic T cells and type-1 T helper cells and activated by IL 12. TNF signalling occurs through two receptors, pro-inflammatory type 1(NFR1) and anti-inflammatory type 2 (TNFR2) receptors. TNFR1 signalling is apoptotic and TNFR2 signalling promotes cell proliferation (Jang *et al.*, 2021).

Therefore, there are delicate checks and balances which limit the production and functions of various cytokines in order to contain viral, bacterial and other pathogens, yet control the collateral damages which may occur during the process (Aggarwal, 2003; Mangalmurti & Hunter, 2020; Jang *et al.*, 2021). Anti-inflammatory cytokines (for example, IL-1 receptor antagonists, IL-4, 6, 10, 11 and 13) are those which control the pro-inflammatory cytokines (cytokine receptors for IL-1, TNFα, IL-18) (Opal & DePalo, 2000).

Cytokine storms refer to an excessive, exaggerated cytokine response or loss of balance or control in the pro-and anti-inflammatory cytokine responses to pathogen invasion. While normally protective, an exaggerated host immune response to COVID-19 infection appeared to underlie some severe cases of COVID-19. Recent studies have shown that impaired response of type-1 IFNs in the early stage of COVID-19 infection played a major role in the development of cytokine storm, and various cytokines, such as IL-6, IL-1, IL-12, TNF (tumour necrosis factor) and IFNγ have been shown to be involved in severe COVID-19 (Alunno *et al.*, 2020; Bhaskar *et al.*, 2020; Cabler *et al.*, 2020; Mangalmurti & Hunter, 2020; Kim *et al.*, 2021; Sette & Crotty, 2021; Yang *et al.*, 2021).

Apart from acute exaggerated cytokine responses resulting in cytokine storms, persistent or lasting elevation of proinflammatory cytokines such as IL-6, IL-1β and TNF are associated with manifestations of long COVID such as enduring neuroinflammation (Mehandru & Merad, 2022) leading to cognitive decline.

Some factors underlying difference in Interferon response between individuals have been discovered. These include autoantibodies against type 1 Interferon (IFN) (Manry *et al.*, 2022), inborn errors in type 1 IFN immunity (Zhang *et al.*, 2020) and IFN resistance of emerging SARS-CoV-2 variants (Guo *et al.*, 2022). Autoantibodies against type I IFNs strongly increased fatality rate at all ages in both men and women and are strong predictors of life-threatening COVID-19 (Manry *et al.*, 2022). Similarities in clinical and cytokine responses between COVID-19 human patients and genetically diverse mouse models have been reported (Robertson *et al.*, 2021). The same group also reported that clinical improvement was correlated with IFN response, as in humans, in that an early IFN response was associated with a rapid viral clearance and mild disease, while a delayed IFN response was associated with viral persistence and inflammation (Rosenthal, 2022). Thus, genetic-based polymorphism in immune responses, at various levels, may explain the differential acute response and later progress in those infected.

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Previous studies in other diseases have already reported the association between genetic polymorphisms in cytokine genes and the susceptibility to inflammatory-related disorders, such as haematologic cancers. For example, Monroy *et al.* (2011) observed that, in combination, allelic variants in the COX2, IL18, ILR4 and IL10 genes modify the risk for developing Hodgkin's disease.

In patients with confirmed COVID-19 infection, high C reactive protein (CRP) level was reported to be strongly associated with severe illness and mortality (C reactive protein level > 200 in 5279 patients reported by Petrilli *et al.*, 2020). Smilowitz *et al.* (2021) measured CRP in 2601 patients with confirmed COVID-19 infection and found CRP level to be strongly associated with venous thrombo-embolism, acute kidney injury, critical illness and mortality. Thus, CRP, as an indicator of inflammation, could be used to measure the degree of systemic inflammation and severity of COVID-19 illness could be stratified to guide therapeutic planning.

Some genes associated with COVID-19 appear to affect the risk of developing autoimmune disease (Verma *et al.*, 2022). Some long COVID cases are characterised by immune dysregulation with autoimmune nature. Autoimmune reactions in adult patients and allergic reactions in children appear to be critical factors (Ortona & Malorni, 2022; Osmanov *et al.*, 2022). Reactivated latent viruses (which may affect long COVID symptoms) may also appear after mild asymptomatic COVID-19 (Apostolou *et al.*, 2022). Historically, immune genes protective against the bubonic plague, especially in Northern European populations, are associated with increased susceptibility to autoimmune diseases (Klunk *et al.*, 2022). It is likely that this susceptibility to autoimmune diseases will affect the appearance of long COVID and should be investigated in more detail.

COVID-19 neuroinflammation

Once a virus has succeeded in entering the body, it triggers off inflammation. At the acute stage, vasculitis is a major pathology, which includes the progression of macro and micro thrombosis, as well as disseminated intravascular coagulation (Asakura & Ogawa, 2021). There was a high rate of coagulopathy reported in COVID-19 patients, with an astonishing rate of venous thromboembolism and pulmonary embolism at 42% and 17%, respectively, in severe cases (Wu *et al.*, 2021). Arterial thrombotic events occur at various sites including coronaries, extremities and importantly, the brain (De Roquetaillade *et al.*, 2021). Neurovascular inflammatory thrombotic events may cause severe damage to the brain at this early stage of COVID-19 with ominous consequences.

While attention was initially focused on vascular inflammation causing thrombosis and carditis (Sawalha *et al.*, 2021), the occurrence of troubling neuropsychiatric symptoms, especially cognitive impairment, was soon called to attention (Ceban *et al.*, 2022; Hugon *et al.*, 2022a). Normally, peripheral-to-brain immune signalling is tightly regulated, but a cytokine storm may lead to a disruption of the blood brain barrier (BBB), resulting in neuroinflammation, encephalopathy and serious neuropsychiatric consequences (Obermeier *et al.*, 2013; Huang *et al.*, 2021; Pensato *et al.*, 2021). Cytokine storm has also been linked to brain pathology such as neurodegeneration, in which elevation of pro-inflammatory cytokine expression, namely IL-1β, has profound effects on synaptic plasticity and, consequentially, cognition (Muscat & Barrientos, 2021).

It is important to mention that Bost *et al.* (2021) described that a lung CXCR6^{+} effector memory T cell subset was associated with better prognosis in patients with severe COVID-19, as COVID-19-induced myeloid dysregulation and lymphoid impairment may establish 'immune silence' in some patients with critical COVID-19, and cytokine storm is avoided (Tang *et al.*, 2020; Zheng *et al.*, 2020). COVID-19 involves marked increases in peripheral IL-6, TNFα, and IL-1β and cytokines are known to have a profound impact on working memory and attention. Cytokines might be key mediators in the aetiology of COVID-19 induced cognitive impairments (Alnefeesi *et al.*, 2021).

Garcia *et al.* (2021) measured cytokines, inflammation and coagulation markers (high-sensitivity-C Reactive Protein [hsCRP], ferritin, fibrinogen, D-dimer, Factor VIII) and neurofilament light chain (NF-L) in 18 COVID-19 subjects with neurological complications. They found that their CSF showed a paucity of neuroinflammatory changes, absence of pleocytosis or specific increases in pro-inflammatory markers or cytokines. Anti-SARS-CoV2 antibodies in CSF of COVID-19 subjects were observed despite no evidence of SARS-CoV2 viral RNA, but CSF-hsCRP was present. They concluded that the data did not support inflammatory neurological complications in COVID-19.

Their data contrasts that of Crunfli *et al.* (2022) who provided evidence that the SARS-CoV-2 virus was indeed present in the human brain, where it infects astrocytes and to a lesser extent, neurons. They showed that astrocytes responded to the infection by remodelling energy metabolism, which in turn, alters the levels of metabolites available to neurons, which then impaired neuronal viability.

'Brain fog' is one of the commonest reported symptoms in long COVID (Chasco *et al.*, 2022) and closely related to chronic neuroinflammation. Subjective changes in brain functions, such as quantitative electroencephalography have been reported (Kopańska *et al.*, 2022). The fatigue and cognitive impairment are similar to that of chronic fatigue syndrome (Azcue *et al.*, 2022) and neuroinflammation is likely the primary cause in both. The neuroinflammatory basis of brain fog in COVID survivors has been compared to that of cancer-therapy induced cognitive impairment, with white matter microglial reactivity and consequent neural dysregulation (Fernández-Castañeda *et al.*, 2022). Chronic cytokinemia affecting BBB permeability, inducing neurotoxicity, plus the generation of autoantibodies resulting in the interference with neurogenesis, neuronal repair, chemotaxis and microglia function naturally would result in cognitive impairment (Elizalde-Díaz *et al.*, 2022).

There is speculative comparison of COVID-19 symptoms to bipolar disorders, citing the commonality of cytokine disorder, sleep disorders, and tryptophan metabolism in both (Lorkiewicz & Waszkiewicz, 2022). ADHD poses increased risk for COVID-19 but may reduce risk of severe outcomes. ADHD medications modestly impacted COVID-19 risk (Heslin *et al.*, 2022). There is obviously a need to separate speculations and solid evidence and how specifically the COVID-19 virus may change the brain and its function in terms of neuropathways.

Hypometabolism and hypermetabolism in brain areas revealed by FDG-PET

New imaging techniques with high sensitivity and specificity are available for the investigation of COVID-19-induced brain changes down to the neurotransmitter and receptor level. These imaging techniques are expensive and complex, requiring teamwork of radiochemists, radiologists and experienced neuropsychiatrists. This, compounded by the polymorphic nature of COVID-19

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inflammation, limits the size of patient inclusion and thus created the difficulty of interpretating highly variable data in small patient samples.

The relatively simple FDG-PET, originally used extensively in neuropsychiatric research, is now standard for diagnosing and staging tumours, monitoring treatment progress and tumour recurrence. Extensive usage of this technique in the past decades has resulted in good standardisation and lowering the costs and complexity of the technique, making this a convenient tool for COVID-19 neuropsychiatric research (Alavi *et al.*, 2021).

The FDG-PET scan technique measures cellular glycolytic activity. F-18 Deoxyglucose accumulates in active cells, and thus, this imaging technique can be used to measure changes in regional brain activity in COVID-19. High or lower activity of the brain area is reflected in higher or lower uptake of the FDG, depicted as a metabolic map of the brain. As inflammatory cells are highly glycolytic, sites of ongoing inflammation are characterised by changes in metabolic activity. Profound recruitment of inflammatory cells such as neutrophils and monocytes also results in metabolic acidosis and lowering availability of oxygen (Kominsky *et al.*, 2010).

Neuropsychiatric symptoms are common in all stages of COVID-19 (reviews by Tang *et al.*, 2021, 2022a). Headache, dizziness, fatigue, cognitive dysfunction such as brain fog and confusion, concentration and memory issues, attention disorder, anxiety and depression, sleep disturbances, hyposmia, anosmia, dysgeusia or ageusia, dysphonia, olfactory dysfunction, numbness and paresthaesia have all been reported (Nataf, 2020; Rogers *et al.*, 2020; Attademo & Bernardini, 2021; Boldrini *et al.*, 2021; Soltani *et al.*, 2021; Taquet *et al.*, 2021). In the review by Premraj *et al.* (2022), which covered 1458 articles and 19 studies, with a total of 11,324 patients, brain fog was found to be as high as 32%, memory issues at 27% and attention disorder at 22%.

It is natural to question if some of the common symptoms in COVID-19, especially in long COVID, such as anxiety and depressed mood, could be psychological (Skyes *et al.*, 2021), reactive or stress related, due to prolonged social or quarantine isolation, loss of income and other psychosocial causes. Brain imaging studies thus may be useful for the evaluation of vague or seemingly psychological symptoms in COVID-19, distinguishing those of transient and psychological nature, from other symptoms of chronic and organic causes, especially at the mid and long COVID stages.

Data from FDG-PET brain imaging studies of COVID-19 patients have been variable (Meyer *et al.*, 2022). 'Hypometabolism' in different brain areas, in different studies, has been reported, but generally in small number of cases. Hypometabolism in the pons was reported in 3 cases with cognitive decline long COVID symptoms (Hugon *et al.*, 2022a) and in the anterior cingulate in another 2 cases with brain fog (Hugon *et al.*, 2022b). Hypometabosim in the right frontal and temporal lobes, including the orbito-frontal cortex and internal temporal areas, was reported in the FDG-PET study of Guedj *et al.* (2021a, 2021b). Asthenia and cardiovascular, digestive and neurological disorders during the acute phase, plus asthenia and language disorders during the chronic phase, were associated with the hypometabolic clusters. Hypometabolism involving bilateral medial temporal lobes, brainstem and cerebellum and the right olfactory gyrus were reported in seven children in the study of Morand *et al.* (2022). In another study consisting of 143 patients, hypometabolic areas were detected in some but not all patients (Verger *et al.*, 2022a, 2022b).

Sollini *et al.* (2021) enrolled 13 adults long COVID patients who complained of at least one persistent symptom for more than 30 days after infection recovery. They reported that long COVID patients exhibited brain 'hypometabolism' in the right parahippocampal gyrus and thalamus. Specific areas of hypometabolism characterised patients with persistent anosmia/ageusia, fatigue and vascular uptake. However, a German group (Dressing *et al.*, 2022) found no significant changes inregional cerebral glucose metabolism in their 14 patients who underwent FDG PET.

There were suggestions that SARS-CoV-2 may preferentially target the frontal lobes, resulting in behavioural and dysexecutive symptoms, as supported by evidence of fronto-temporal 'hypoperfusion' on MRI, EEG slowing in frontal regions and frontal hypometabolism on FDG-PET (Toniolo *et al.*, 2021).

Kas *et al.* (2021) investigated seven patients with variable clinical presentations of COVID-19-related encephalopathy and predominant cognitive and behavioural frontal disorders, at the acute phase, 1 and 6 months after COVID-19 onset. Importantly, SARS-CoV-2 RT-PCR in the CSF was negative for all patients. Again, all patients showed 'hypometabolism' in a widespread cerebral network, including the frontal cortex, anterior cingulate, insula and caudate nucleus. At 6 months, the majority of patients still had prefrontal, insular and subcortical 18F-FDG-PET/CT abnormalities, with cognitive and emotional disorders of varying severity and attention/executive disabilities and anxio-depressive symptoms (Kas *et al.*, 2021).

Martini *et al.* (2022) studied 26 patients with neurological symptoms using FDG-PET. The 'fronto-insular cortex' again emerged as the 'hypometabolic' hallmark of neuro-COVID-19. Acute patients showed the most severe hypometabolism affecting several cortical regions. Three-month and 5-month patients showed a progressive reduction of hypometabolism, with limited frontal clusters. After 7–9 months, no brain hypometabolism was detected. Another patient evaluated longitudinally showed a diffuse brain hypometabolism in the acute phase and almost recovered after 5 months. Brain hypometabolism is correlated with cognitive dysfunction, low blood saturation and high inflammatory status. Interestingly, they found 'hypermetabolism' in the brainstem, cerebellum, hippocampus and amygdala, which persisted over time and correlated with inflammation status. Goehringer *et al.* (2022) reported extensive hypometabolic right fronto-temporal clusters in 28 outpatients with post-COVID-19 condition. Those with more symptoms and of longer duration during the initial phase were at higher risk of persistent brain involvement.

The above metabolic changes revealed by FDG-PET may be compared with other inflammatory neuropsychiatric disorders such as encephalitis. For example, Wei *et al.* (2020) reported frontal-dominant 'hypometabolism' in a 66-year-old female patient with anti-AMPAR encephalitis but an occipital-dominant hypometabolism in a 29-year-old female patient with anti-NMDAR encephalitis. Receptor density maps revealed opposite frontal-occipital gradients of AMPAR and NMDAR, which reflect reduced metabolism in the correspondent encephalitis. They suggested that FDG-PET hypometabolic areas may represent receptor hypofunction, with spatial correspondence to receptor distributions of autoimmune encephalitis. In summary, the six features of metabolic anomalies of autoimmune encephalitis included: (a) temporal hypermetabolism, (b) frontal hypermetabolism and (c) occipital hypometabolism in anti-NMDAR encephalitis, (d) hypometabolism in association cortices, (e) sparing of unimodal primary motor cortex and (e) reversibility in recovery. These six features may be

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used to interpret COVID-19 hypo and hyper metabolic brain changes.

It may be useful to mention the data of Zhao *et al.* (2021). They studied 25 patients with anti-LGI1 encephalitis and found subcortical hypermetabolism associated with cortical hypometabolism to be a common metabolic pattern in patients with anti-LGI1 encephalitis. Lagarde *et al.* (2016) reported cerebral FDG-PET data in six paediatric patients with confirmed anti-NMDAR encephalitis of severe course. Four patients were normal in MRI imaging but all six patients showed extensive, symmetric cortical hypometabolism especially in posterior areas; asymmetric anterior focus of hypermetabolism and basal ganglia hypermetabolism. They also found a good correlation between the clinical severity and the cerebral metabolism changes and serial cerebral FDG-PET showed parallel brain metabolic and clinical improvement.

FDG-PET has proven its value in other neuropsychiatric inflammatory disorders, such as autoimmune encephalitis (Bordonne *et al.*, 2021), including suspected COVID-19 autoimmune disorders. It may be positioned as an early biomarker of disease so that treatment may be initiated earlier (Solnes *et al.*, 2017).

In summary, brain imaging tools, especially FDG-PET, are useful for the investigation of brain functional changes in COVID-19. The contrasting or conflicting brain imaging results also raised the possibility that brain hypometabolic changes in patients infected with the SARS-CoV-2 virus also showed great inter-individual differences, similar to other clinical data such as the percentage of asymptomatic cases. Inflammatory polymorphism again may explain the aberrations.

FDG-PET combined with other technology

Other radioactive ligands to study receptor changes have been proposed as well but the techniques are still in the developing stage. Various techniques have been attempted for the study of neuroinflammation. It would be interesting to mention the study by Brusaferri *et al.* (2022), who used simultaneous PET and MRI to study links between pandemic-related stressors and neuroinflammation. The translocator protein TSPO and myoinositol are two glial neuroinflammatory markers that can be detected with PET and MR spectroscopy, respectively. Healthy individuals examined after the enforcement of 2020 lockdown demonstrated elevated brain levels of both neuroinflammatory markers compared to pre-lockdown subjects. Subjects with higher symptom burden showed higher TSPO signal in the hippocampus (mood alteration, mental fatigue), intraparietal sulcus and precuneus (physical fatigue), compared to those reporting little or no symptoms. This raises another complexity in interpretation of brain scan data, which is the confounding nature of psychological reaction and neuroimmune activation in COVID-19. Gouilly *et al.* (2022) raised a concern in the interpretation of the translocator protein TSPO. He was of the opinion that although neuroinflammation is a significant contributor to Alzheimer's disease (AD), and that PET imaging of (TSPO) had been widely used to depict the neuroimmune endophenotype of AD, the biological basis of the TSPO PET signal is more related to microglia and astrocytes in AD and might not be directly related to neuroinflammation proper.

Magnetic resonance brain scan

Douaud *et al.* (2022) investigated brain changes in 401 COVID-19 cases who tested positive for infection with SARS-CoV-2 between their two scans, compared to 384 controls. They found reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex and reduction in global brain size. There was a greater cognitive decline between the two time points. They proposed a degenerative spread of the disease through olfactory pathways of 'neuroinflammatory' events.

Postmortem and animal studies

Matschke *et al.* (2020) reported their postmortem findings in 43 patients (age 51−4). They found fresh territorial ischaemic lesions in six patients and 37 (86%) patients had astrogliosis in all assessed regions. Activation of microglia and infiltration by cytotoxic T lymphocytes was most pronounced in the brainstem and cerebellum, and meningeal cytotoxic T lymphocyte infiltration was seen in 34 (79%) patients. SARS-CoV-2 could be detected in the brains of only about half of the patients, but SARS-CoV-2 viral proteins were found in cranial nerves originating from the lower brainstem and in isolated cells of the brainstem. The presence of SARS-CoV-2 in the CNS was not associated with the severity of neuropathological changes. Thus, neuropathological changes in patients with COVID-19 seem to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding.

Fabbri *et al.* (2021) reported brain ischaemic injuries in 10 postmortem cases. All showed extensive microthrombi and recent infarcts in the basal ganglia and the brainstem. Their findings are in keeping with the hypercoagulable state ending in thrombosis.

Other new animal postmortem studies may shed light on mechanisms underlying COVID neuroinflammation. In a non-human primate model, SARS-CoV-2 virus was found in the olfactory cortex and interconnected regions at 7 days post-infection. Neurocovid here is accompanied by robust neuroinflammation and vascular disruption, with greater brain pathology in aged and diabetic monkeys (Beckman *et al.*, 2022).

Alpha-synuclein, a protein involved in Parkinson's disease, appears to be an important player in neuronal immune response. Parkinsonism and neurological manifestation of influenza throughout the 20th and the 21st centuries have been discussed (Henry *et al.*, 2010). Alpha-synuclein supports type 1 interferon signalling in neurons and its expression restricts RNA viral infection in the brain (Beatman *et al.*, 2015; Massey & Beckham, 2016). Mice lacking alpha-synuclein expression exhibit markedly increased viral growth in the brain, increased mortality and increased neuronal death (Monogue *et al.*, 2022). In a Syrian golden hamsters COVID model, persistent brain pathology occurred despite the clearance of virus. It seems that viral protein in the nasal cavity led to pronounced microglia activation in the olfactory bulb. Cortical but not hippocampal neurons accumulated hyperphosphorylated tau and alpha-synuclein, in the absence of visible inflammation and neurodegeneration, suggesting selective vulnerability (Käufer *et al.*, 2022). Rosen *et al.* (2021) have described the numerous similarities between neurodegeneration in Parkinson's disease and RNA viral infections, including SARS-CoV-2. Idrees and Kumar (2021) have reported that the SARS-CoV-2 S1 receptor binding domain binds to a number of aggregation-prone, heparin-binding proteins including Aβ, α-synuclein, tau, prion, and TDP-43 RRM. These interactions suggest that the heparin-binding site on the S1 protein might assist the binding of amyloid proteins to the viral surface and thus could initiate aggregation of these proteins, finally leading to neurodegeneration in the brain. Indeed, interactions between SARS-CoV-2 N-

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protein and α-synuclein have been found to accelerate amyloid formation (Semerdzhiev *et al.*, 2022). Wu *et al.* (2022b) have reported that SARS-CoV-2 proteins caused Lewy-like pathology in the presence of α-synuclein overexpression. It seems wise to continue long-term surveillance of COVID-19 patients to see if susceptible individuals develop further neurodegenerative disorders (Leta *et al.*, 2022).

Neurotransmitters and receptors in COVID-19

Investigation of neurotransmitter and receptor changes in COVID-19 has not been studied in great detail yet. In vivo brain imaging approaches are limited by the costs and technological complexity of radioisotope ligand labelling beyond the common F18-FDG metabolic scanning approach.

The observation of SSRI antidepressant drugs modulating the severity of COVID-19 has raised interest in the role of serotonin (Attademo & Bernardini, 2021; Ha *et al.*, 2021; Sadlier *et al.*, 2022) and sigma receptors.

SARS-CoV-2 is likely to induce oxygen dysmetabolism in neuronal cells, and the PET radiotracer [^{15}O]O2 may help us to examine the prevalence of hypoxia in the brain of COVID-19 patients. Fontana *et al.* (2020) also proposed the use of other PET tracers to study neurotransmitters and their receptor changes in COVID-19. For example, including [^{11}C]ABP688, for the metabotropic glutamate receptor 5 (mGluR5), [^{11}C]Flumazenil PET radiotracer to access the availability of the α subunits of the $GABA_A$ receptor, and [^{18}F]FEOBV for potential cholinergic deficits, [^{11}C]DASB for the serotonin transporter (SERT), [^{18}F]FDOPA as a marker of dopaminergic cells. Neuroinflammatory changes can be assessed, for instance, using [^{11}C]PK11195, a widely used radiotracer to track microglial activation, and [^{11}C]DED, a radiotracer for detecting reactive astrogliosis.

Age, gender and related immune status underlying COVID-19-related neuroinflammation

COVID-19 infection appeared to be only mild to moderate in the majority of healthy individuals but does cause life-threatening disease or persistent symptoms in others. One of the most important determinants of disease severity is age (Brodin, 2021; Costagliola *et al.*, 2021).

At the early stage of COVID-19, children were thought to be largely immune and if infected, would suffer only mild symptoms (Götzinger *et al.*, 2020; Guan *et al.*, 2020). More cases of COVID-19 in children have begun to be reported recently (Nikolopoulou & Maltezou, 2022). The relatively immature immunological apparatus and thus less tendency for uncontrolled or exaggerated inflammatory response such as cytokine storms (Palmeira *et al.*, 2020; Wong *et al.*, 2020; Yasuhara *et al.*, 2020) was originally claimed to be the explanation. This proves later to be a more complex situation, with an increase in paediatric COVID-19 patients suffering from multi-system inflammation with ominous outcomes (Dufort *et al.*, 2020; García-Salido *et al.*, 2020; Pereira *et al.*, 2020; Swann *et al.*, 2020; Wong *et al.*, 2022).

The new syndrome that occurs in children exposed to COVID-19, called 'multisystem inflammatory syndrome' or MIS (Whittaker *et al.*, 2020), is becoming a concern. Childhood MIS reminds us of the well-known Kawasaki disease (Rife & Gedalia, 2020). They seem to share some similarities with regard to the pathology and immune responses (Cattalini *et al.*, 2021; Cheung *et al.*, 2020; Chen *et al.*, 2021; Hernandez *et al.*, 2021; McCrindle & Manlhiot, 2020; Singh-Grewal *et al.*, 2020; Yasuhara *et al.*, 2020; Mercier *et al.*, 2021; Zhang *et al.*, 2021). In COVID-19, MIS is now considered as the cytokine storm manifestation in children (Zhang *et al.*, 2021; Zimmermann *et al.*, 2021; Brodin, 2022). In this regard, genetic susceptibility to MIS (haploinsufficiency of suppressor of cytokine signalling 1 (SOCS1), a negative regulator of type I and II interferons) has been reported by Chou *et al.* (2021).

On the other hand, the aged, particularly men, have always been known to be vulnerable, with the greatest risk of requiring intensive care. Their vulnerability may be related to their less effective, inadequate, or unstable immunological systems (Liang, 2020; Williamson *et al.*, 2020; Gallo Marin *et al.*, 2021), though some might have pre-existing compromised pulmonary and cardiovascular functions. Obesity, older age, cardiovascular comorbidities, pre-existing pulmonary condition, and chronic kidney disease, among other factors, are all associated with increased risk of hospitalisation, mechanical ventilation and mortality (Feng *et al.*, 2020; Klang *et al.*, 2020; Williamson *et al.*, 2020). Long COVID, on the other hand, appears to be more prevalent in women than in men (Brodin, 2021; Skyes *et al.*, 2021).

With regard to the age factor, the immune system undergoes a complex process of maturation from birth to adult age. Differences in the immune and inflammatory response between individuals are important in determining the spectrum of severity of COVID-19. Children show a higher ability to respond to viral infections but a reduced baseline pro-inflammatory state compared with elderly patients.

Exaggerated immune response, especially in the form of a cytokine storm, is associated with high morbidity and mortality (Alunno *et al.*, 2020; Cabler *et al.*, 2020; Sawalha *et al.*, 2021; Sette & Crotty, 2021; Yang *et al.*, 2021). Cytokine storm is itself polymorphic (Alunno *et al.*, 2020). In children, when developed, cytokine storm appeared to be different from that occurring in the adult. The MIS in children 4–6 weeks after infection (Mid COVID) has overlapping features with Kawasaki disease. Autoantibody profiling suggests multiple autoantibodies. The inflammatory response in MIS differs from the cytokine storm of acute COVID-19. While sharing some features with Kawasaki disease, it also differs with respect to T cell subsets, interleukin (IL)-17A, and biomarkers associated with arterial damage (Consiglio *et al.*, 2020; Brodin, 2022). MIS could be the result of repeated release of viral protein from a SARS-CoV-2 viral reservoir and a superantigen motif of the SARS-CoV-2 spike protein (Kouo & Chaisawangwong, 2021; Brodin & Arditi, 2022; Noval Rivas *et al.*, 2022) leading to a broad non-specific T-cell activation.

Treatment

Accepting that inflammation plays a major role in causing morbidity and mortality in COVID-19, treatment naturally focuses on inflammation and immunomodulation at every stage of COVID-19 infection (Rommasi *et al.*, 2022). Antiviral therapies, anti-ACE-2 and SARS-CoV-2 viral binding/docking agents, thrombosis treatment and cytokine storm management (Stebbing *et al.*, 2020; Hu *et al.*, 2021; Karki & Kanneganti, 2021), adjusted to the severity of COVID-19 symptoms are important in this acute stage before the beginning of inflammation, or to advert a full-scale inflammatory response. Anti-inflammatory and immunomodulatory therapies continue to be important in the mid stage. Many long COVID symptoms are neuropsychiatric in nature, such as cognitive and memory impairment. Search for new agents or repurposing drugs to reactivate impaired neuronal functions, or hypometabolic brain areas are just in the beginning. Careful neuropsychiatric evaluation, including investigations such

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as FDE-PET brain scans, may be useful. Reviews of pharmacological treatment of COVID-19 are plentiful (Zheng *et al*., 2020; García-Lledó *et al*., 2022; Rommasi *et al*., 2022).

Early-stage Blockade of Viral entry via Spike protein- ACE-2 interaction

At the early viral entry stage, direct elimination of virus with antiviral drugs and blockade of entry or interference with viral binding to the ACE-2 receptors can be attempted, such as nasal spray-based vaccines. Neutralising antibodies against the Spike protein of the virus, drugs targeting the ACE-2 gene expression and agents that decrease ACE-2 expression in respiratory tract epithelium are in development, including agents that target epigenetic mechanisms such as DNA methylation and epitranscriptomic mechanisms. Removal of excessive cytokines through dialysis to modulate a cytokine storm has also been proposed (Kim *et al*., 2021).

Sigma-1 receptor agonists

Ostrov *et al*. (2021) have reported that highly specific sigma receptor ligands may exhibit anti-viral properties in SARS-CoV-2 infected cells. Preliminary data raised the possibility that some antidepressant drugs such as fluvoxamine, may prevent severe impairment (Gordon *et al*., 2020; Lenze *et al*., 2020; Bora *et al*., 2021; Hoertel *et al*., 2021) intubation or death in COVID-19.

It is possible that blockade of viral activities in the ER could be accomplished with molecules targeting the sigma receptor (Hashimoto, 2021). Sigma receptor agonists such as fluvoxamine, (Khani & Entezari-Maleki, 2022), Ayahuasca (a folk lore herbal drink containing b-carbolines), *N*,*N*-dimethyltryptamine (DMT), a sigma agonist (Escobar-Cornejo *et al*., 2022) all potentially could be repurposing for the management of SARS-CoV-2 infection by blocking the interaction of the virus with sigma receptor (Vela, 2020; Tang *et al*., 2022b).

However, prescribing antidepressants to COVID-19 patients has been cautioned (Borovcanin *et al*., 2022) and antidepressants may also induce dangerous mood switching in patients with mood disorders (see review by Tang *et al*., 2022b).

Other ACE-2 blockers

Apart from sigma-1 receptor molecules, other drugs, molecules and herbal ingredients have also been reported to interfere with the spike protein binding to the ACE-2 receptors and molecular docking technology may identify new and effective agents targeting the viral spike protein, ACE-2 receptors, or both (Gao *et al*., 2020; Wang & Yang, 2021; Ye *et al*., 2021).

There are interesting reports on cannabinoids from Cannabis Sativa for their anti-covid-19 properties. To date these studies have mostly been restricted to cellular-based in vitro studies (Raj *et al*., 2021). The most potent anti-viral properties were shown by tetrahydrocannabinol (THC) and cannabindiol (CBD) compared to the reference drugs lopinavir and remdesvir. Unlike THC, because of its non-addictive properties, studies have concentrated on CBD (Corpetti *et al*., 2021; Suryavanshi *et al*., 2022; Vallée, 2022), which was shown to potently inhibit the ACE-2 receptor via the AKT inflammatory pathway (Wang *et al*., 2022c). The cannabinoid acids (cannabigerolic acid and cannabiolic acid) have a micromolar affinity for the covid-19 spike protein and were equally effective against the alpha- and beta-SARS-COV2 variants. This may imply that some cannabinoids have the potential to both prevent and treat the covid-19 infection (van Breemen *et al*., 2022).

Research on the cannabinoids to treat covid-19 is still in its early stages and detailed clinical studies are essential. However, Nguyen *et al*. (2022) reported that patients from the National Covid Cohort Collaborative CBD study showed a significant negative association with the positive covid-19 test for infection.

Anti-inflammatory or inflammation modulatory agents

The role of anti-inflammatory agents as preventive measures and treatment is the main foci in COVID-19 management (Soy *et al*., 2020).

Biologics

Most COVID-19 patients, especially among elderly patients, had marked lymphopenia and increased neutrophils, although T cell counts in severe COVID-19 patients surviving the disease may gradually be restored. Elevated pro-inflammatory cytokines, particularly IL-6, IL-10, IL-2 and IL-17, and exhausted T cells are found in peripheral blood and the lungs.

It was suggested that convalescent plasma, IL-6 blockade, mesenchymal stem cells and corticosteroids may suppress cytokine storm (Luo *et al*., 2021; Zanza *et al*., 2022). Tocilizumab (monoclonal antibody against IL-6 receptors) if given early has been shown to block cytokine storms (Xu *et al*., 2020; Gupta *et al*., 2021; Kulanthaivel *et al*., 2021). The REMAP-CAP trial evaluated 6 treatment classes for 4689 intensive care COVID-19 patients and confirmed a substantial clinical benefit of the IL-6 receptor antagonists tocilizumab and sarilumab. This same study also was unable to confirm the claimed benefits of convalescent plasma exchange, the anti-malarial hydroxychloroquine (might even be harmful), nor the anti-viral lopinavir and ritonavir (Barnett & Sax, 2023).

Many other anti-inflammatory and anti-cytokine agents or inflammation-modulating biologics (Jones *et al*., 2021; Arias *et al*., 2022), such as anti-IL-1 agent Anakinra, have been tried in severe COVID. It is quoted that there are more than 150 clinical trials on biologic therapy for COVID-19 in progress (González-Gay *et al*., 2021). Optimal brain function depends on TNF. Etanercept, a recombinant inhibitor of TNFα, has been used to modulate the excess TNF level in COVID neuroinflammation, resulting in improvement in cognitive and other brain dysfunctions, depression and fatigue in long COVID (Chen *et al*., 2020; Clark, 2022; Duret *et al*., 2020; Tobinick *et al*., 2022).

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NSAIDs

The benefits of anti-inflammatory agents (Aspirin and other NSAIDs, herbal medicine, and other anti-inflammatory agents) and immune-modulatory agents such as corticosteroids in COVID-19 have been widely reported, though their efficacy and use in different stages still need to be confirmed (Chow *et al*., 2021; RECOVERY Collaborative Group *et al*., 2022; Salah & Mehta, 2021; Srivastava & Kumar, 2021; Zareef *et al*., 2022).

Initially, nonsteroidal anti-inflammatory drugs (NSAIDs) had been discouraged for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. In April 2020, French authorities issued warnings regarding the use of ibuprofen with other NSAIDs in patients with COVID-19 symptoms. Moore *et al*. (2021) reviewed existing reports on the use of ibuprofen in COVID-19 but was unable to confirm that ibuprofen increased the risk of COVID-19. This was confirmed in many other reports. Ibuprofen continues to be recommended for use in managing COVID-19 symptoms (Poutoglidou *et al*., 2021).

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NSAIDs as a group do not increase the risk and/or severity of COVID-19 (Prada *et al.*, 2021; Zhao *et al.*, 2022). Similarly, the use of NSAIDs was not associated with 30-day mortality, hospitalisation, ICU admission, mechanical ventilation or renal replacement therapy (Lund *et al.*, 2020). Use of ibuprofen and COX-2 inhibitors was not associated with an increased risk of death (Zhou *et al.*, 2022). Prior use of NSAIDs was associated with a decreased risk of severe COVID-19, but there is an increased risk of stroke also.

Osborne *et al.* (2021) studied patients with and without active aspirin prescription before acquiring SARS-CoV2. They found aspirin users had a significantly decreased risk of mortality after infection. Similar results were reported by many others (Haji Aghajani *et al.*, 2021; Liu *et al.*, 2021). However, these observations contradict the results of the RECOVERY trial, which did not find a correlation between aspirin intake and 28-day mortality, nor significant difference in the outcome of mechanical ventilation or death within 28 days of admission (RECOVERY Collaborative Group *et al.*, 2022). The REMAP-CAP trial found aspirin or P2Y12 inhibitors (antiplatelet agents) demonstrated a high likelihood of improving 180-day mortality. Comparatively, anticoagulation with heparin in noncritical disease of moderate severity, but not in critical disease, improved outcomes (Barnett & Sax, 2023).

The risks of gastric irritation, bleeding, and Reye's syndrome associated with aspirin usage in children (Schrör, 2007) should all be considered when NSAIDs such as Aspirin and Ibuprofen are administered as anti-inflammatory agents.

COX-2 inhibitors

There is substantial data showing that COX-2 is involved in cytokine storms. COX-2 is induced by cytokines and inflammatory mediators, resulting in the release of prostaglandin E2 (PGE2). NSAIDs act via inhibition of COX-1 and 2 activities. This leads to decreased (PGE2) production. The selective COX-2 inhibitor Celecoxib is a popular NSAID. It is metabolised primarily by CYP 2C9. Apart from the long-term cardiovascular and gastrointestinal bleeding risks, many drugs, including psychiatric drugs such as valproic acid, are CYP2C9 substrates or inhibitors, and potential drug–drug interactions may occur. AlAjmi *et al.* (2021) also cautioned that Celecoxib is a TNFα-converting enzyme (TACE) inhibitor and may aggravate COVID-19. The enzyme TACE is responsible for converting membrane-bound ACE-2 receptors into soluble ACE-2. Inhibition of TACE would lead to an increased population of membrane-bound ACE-2 and may facilitate viral entry. Four drugs (Celecoxib, Glipizide, Lapatinib and Sitagliptin) have been identified as potential inhibitors of TACE. However, their binding affinities are in the micromolar range, which may be outside the normal therapeutic range.

Dexamethasone and other immune-modulating agents

Although the use of glucocorticoids in COVID-19 has been common, the place of glucocorticoids in COVID-19 is complex. Recently, there was a proposal that endogenous glucocorticoids may interfere with the binding of the viral spikes to the ACE-2 receptors (Hardy & Fernandez-Patron, 2022; Sarker *et al.*, 2022). There are new in vitro reports demonstrating the effect of corticosteroids on the immune cells, which may be the basis of its action in modulating the cytokine storm (Morrissey *et al.*, 2021).

Patients with COVID-19 mount an acute cortisol stress response. High cortisol concentrations have been found to be associated with increased mortality and a reduced median survival. Tan *et al.* (2020b) found that a doubling of cortisol concentration was associated with a significant 42% increase in mortality risk. Güven and Gültekin (2021) reported that very high cortisol levels are associated with severe illness and increased risk of death in ICU patients.

It is important to caution that administration of glucocorticoids may activate Epstein Barr Virus lytic replication through the upregulation of immediate early BZLF1 gene expression (Yang *et al.*, 2010). To mitigate this, designing new 'dual pan antiviral and anti-cytokine storm agents' have been proposed (Speck-Planche & Kleandrova, 2022). General antivirals which act against more than one virus, for example, Epstein Barr Virus (EBV), in addition to COVID-19, have also been investigated, especially if EBV reactivation is responsible for some long COVID symptoms (Gold *et al.*, 2021). EBV can be reactivated as a result of a variety of stressor events (Sausen *et al.*, 2021). Long COVID has lower cortisol levels versus controls (Klein *et al.*, 2022). Su *et al.* (2022) have identified multiple early factors which anticipate post-acute COVID-19 sequelae, namely EBV-reactivated auto-antibodies, type 1 diabetes and COVID-19 RNAemia.

The efficacy of glucocorticoids has been tested widely in COVID-19 (Attaway *et al.*, 2021). It is also commonly used to treat anosmia and dysgeusia. It has been reported that those who received fluticasone nasal spray and triamcinolone medications recovered their senses of taste and smell within a week (Singh *et al.*, 2021). While this obviously needed to be confirmed, it does support the inflammatory basis of anosmia.

Dexamethasone has been shown to significantly reduce the mortality rate among severe COVID-19 cases (Noreen *et al.*, 2021). Numerous cases have been reported to benefit from the early use of corticosteroids in reversing the occurrence of cytokine storms (Kolilekas *et al.*, 2020; Wagner *et al.*, 2021). However, Jamaati *et al.* (2021) found corticosteroid administration had no clinical benefit in patients with COVID-19. In a more recent review, Zhou *et al.* (2022b) showed a significant association between dexamethasone use and reduced risk of in-hospital mortality for those not receiving remdesivir and a borderline statistically significant risk for those receiving remdesivir. Similarly, the use of dexamethasone was found to lower 28-day mortality in the RECOVERY Collaborative Group study. However, the benefit occurred only among those who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support (Horby *et al.*, 2021).

Thus, the benefit of corticosteroid treatment remains controversial. Its efficacy, indications, and optimal dosage will need to be examined further (Akter *et al.*, 2022).

Colchicine

Colchicine is one of the oldest anti-inflammatory agents (Chiu *et al.*, 2021) and is reported to be useful in COVID-19 to reduce hospitalisation time and mortality rate (Golpour *et al.*, 2021; Pelechas *et al.*, 2021; Vitiello & Ferrara, 2021). Colchicine can target multiple mechanisms associated with COVID-19's excessive inflammation. Successful outpatient treatment of COVID-19 with colchicine could greatly reduce morbidity, mortality and the demand for expensive care resources (Reyes *et al.*, 2021).

Colchicine 1 mg for 1–3 days followed by 0.5 mg/day for 14 days was found to be effective as a proactive anti-inflammatory therapy in hospitalised patients with COVID-19 and viral pneumonia (Mareev *et al.*, 2021).

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Histamine and Antihistamine agents in COVID-19

Histamine participates in bidirectional messaging between cytokines and inflammatory cells or their precursors, facilitates migration of cells to inflammatory sites, stimulates lymphocyte activity, modulates aspects of eosinophil, neutrophil and mast cell behaviour and is directly implicated in the generation of cardinal allergic symptoms (Canonica & Blaiss, 2011). In the CNS, microglial activation is regulated by histamine, leading to the production of proinflammatory cytokines, such as IL-6 and TNF-α (Dong *et al*., 2014). Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19 (Conti *et al*., 2020).

Histamine exerts a complex effect on the immune system through its four histamine GPCRs (G protein-coupled receptors). There are four HRs (1–4) known so far (see review by Branco *et al*., 2018). HR1–3s are widely distributed in neurons, astrocytes and blood vessels. Stimulation of H1R and H2R appear to favour and H3R dampens neuroinflammation through modulation of chemokines production and blood-brain barrier permeability; antagonism of H4R increases inflammatory mediators. The H_1-histamine receptor is most clearly associated with modulation of proinflammatory immune cell activity. The second-generation antihistamines such as loratadine, cetirizine, were highly selective for the H1 receptor whereas the third-generation antihistamines, which are either active metabolites (i.e. desloratadine, fexofenadine) or enantiomers (levocetirizine) of second-generation compounds exhibit even more potent H1-receptor antagonist and anti-inflammatory activity than their parent compounds. These new antihistamines are widely used in relieving allergic symptoms clinically and some have been shown to possess anti-inflammatory action as well and tested in COVID-19.

Dual-histamine receptor blockade with cetirizine – famotidine reduces pulmonary symptoms in COVID-19 patients (Hogan *et al*., 2020). Famotidine activates the vagus nerve inflammatory reflex to attenuate cytokine storm (Yang *et al*., 2022). It is not clear yet whether histamine H1 and H2 antagonists differ in their immunomodulatory efficacy. This will have to be explored in further clinical trials. Reznikov *et al*. (2021) identified antihistamine candidates by mining electronic health records of more than 219,000 subjects tested for SARS-CoV-2. They found diphenhydramine, hydroxyzine and azelastine to exhibit direct antiviral activity against SARS-CoV-2 in vitro, whereas hydroxyzine, and possibly azelastine, bind Angiotensin Converting Enzyme-2 (ACE2) and the sigma-1 receptors.

There have been discussions about whether antihistamines are also anti-inflammatory (Assanasen & Naclerio, 2002; Tsicopoulos & Nadai, 2003) because histamine influences cell types that govern immune and inflammatory reactions. The anti-allergic properties of antihistamines usually refer to their ability to inhibit mast cell and basophil activity. These are linked to the early-phase inflammatory reaction. However, more later-generation H_1-antihistamines such as desloratadine, were demonstrated to inhibit basophil cytokines such as IL-4 and IL-13 (Schroeder *et al*., 2001) and capable of intervening at various points in the immune cascade (Agrawal, 2004; Malone *et al*., 2020). Reports of favourable responses to histamine receptor antagonists since the beginning of COVID-19 seemed to suggest a mechanism that is distinct from anaphylaxis and likely to be related to histmaine's effect on the T cells (Kmiecik *et al*., 2012). T cell perturbations have been reported to persist for several months after mild COVID-19 and are associated with long COVID symptoms (Glynne *et al*., 2022).

Antihistamines and glucocorticoids (GCs) are sometimes used together in the treatment of inflammation. Zappia *et al*. (2021) have demonstrated that all antihistamines potentiate GCs' anti-inflammatory effects in vitro, presenting ligand-, cell- and gene-dependent effects. The combination of antihistamines and corticosteroids in COVID-19 should be tested.

Vitamin B12

Using a computational approach, Pandya *et al*. (2022) demonstrated that vitamin B12 resulted in significant binding with furin. Furin, a protease, has been shown to be important for SARS-CoV-2 infectivity and entry into the host cells in vitro (Essalmani *et al*., 2022; Lavie *et al*., 2022; Takeda, 2022).

The data of Dalbeni *et al*. (2021) do not support a potential therapeutic role of B12 supplementation without B12 deficiency. On the contrary, they found a potential association between high plasma levels of vitamin B12 and increased risk of mortality. Moreover, the cyanocobalamin fraction of B12 may worsen prognosis of renal insufficiency patients.

Vitamin B12 benefits (Tan *et al*., 2020; Wee, 2021; Batista *et al*., 2022) but also may associate with poor outcomes (Dalbeni *et al*., 2021. A vitamin D/magnesium/vitamin B_{12} combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support, intensive care support, or both. This study supports further larger randomised controlled trials to ascertain the full benefit of this combination in ameliorating the severity of COVID-19 (Tan *et al*., 2020).

Vitamin D

There are many reports demonstrating the beneficial usage of vitamin D in COVID-19 (Annweiler *et al*., 2020; Mohan *et al*., 2020; Hadizadeh, 2021; Ismailova & White, 2022). Vitamin D was identified as one of the top three molecules showing potential COVID-19 infection mitigation patterns (Glinsky, 2020). The benefits included fewer rates of ICU admission, few severe cases, mortality events, and RT-PCR positivity (Annweiler *et al*., 2020; Bilezikian *et al*., 2020; Abdollahi *et al*., 2021; Bae *et al*., 2022; Ismailova & White, 2022; Shah *et al*., 2022; Pal *et al*., 2022; Pereira *et al*., 2022; Varikasuvu *et al*., 2022; Wang *et al*., 2022).

Vitamin D enhances and modulates the immune system to arrest or dampen damage caused by cytokine storm (Ali, 2020; Grant *et al*., 2020; Mercola *et al*., 2020; Hadizadeh, 2021). Vitamin D is also neuroprotective (Xu *et al*., 2020) and deficiency is associated with increased autoimmunity (multiple sclerosis and rheumatoid arthritis as two examples) as well as increased susceptibility to infection (Aranow, 2011).

On the other hand, Vitamin D increases the bioavailability and expression of ACE-2, which may trap and inactivate the virus. In conclusion, vitamin D defends the body against SARS-CoV-2 through a novel complex mechanism that operates through interactions between the activation of both innate and adaptive immunity, ACE-2 expression and inhibition of the RAS system (Peng *et al*., 2021).

Some recommended that people at risk of influenza and/or COVID-19 consider taking a mega dose of 10,000 IU/d of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d (Grant *et al*., 2020). The goal is to raise 25(OH)D concentrations about 40–60 ng/ml) (Bae *et al*., 2022). Oristrell *et al*. (2022) analysed the associations between cholecalciferol or calcifediol supplementation, serum 25-hydroxyvitamin D (25OHD) levels and COVID-19 outcomes in a large population

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supplemented with cholecalciferol or calcifediol. They observed that those patients supplemented with cholecalciferol or calcifediol achieving serum 25OHD levels ≥ 30 ng/ml had better COVID-19 outcomes.

No studies to date have found that vitamin D affects post-COVID-19 symptoms or biomarkers (Barrea *et al.*, 2022).

Herbal medicine

Herbal medicine is popular in many countries and has a long history of usage in viral diseases in the East (Ang *et al.*, 2022; Wu *et al.*, 2022). Some herbal preparations, especially the Lianhua Qingwen Capsules, have been shown to have therapeutic effects on COVID-19 (Balkrishna *et al.*, 2021; Shi *et al.*, 2022; Wang *et al.*, 2022b). Many such herbal preparations contain significant anti-viral and immune-modulating molecules (Boozari & Hosseinzadeh, 2021; Han *et al.*, 2021). Lianhua Qingwen Capsules was used previously to treat SARs and later for influenza and other viral infections. They contained a mixture of 11 herbs. The active molecules included quercetin, kaempferol, luteolin, β-sitosterol, indigo, wogoni and other anti-inflammatory and anti-viral compounds. They have modulating effects on multiple immune factors and targets, including ACE-2 receptors (Shen & Yin, 2021).

Natural compounds which interfere with the binding of the viral spike protein to ACE-2 receptors may also be discovered through molecular docking analysis (Gao *et al.*, 2020; Pokhrel *et al.*, 2021; Wang & Yang, 2021; Ye *et al.*, 2021). Other natural compounds may induce epigenetic silencing of ACE-2 gene and that includes the DNA methyltransferase inhibitor curcumin, 8-hydroxyquinolones and sulforaphane (Chlamydas *et al.*, 2021).

Conclusion

From the literature review, it appears that there is strong evidence now to support the view that inflammation is an important factor in deciding the pathology, progression, treatment and prognosis of the spectrum of COVID-19 diseases. Inter-individual differences in inflammatory responses determine the symptoms, morbidity and mortality in COVID-19. Anti-inflammatory managment with anti-inflammatory and inflammatory modulatory agents, not currently standard of care in the management of critical COVID-19, may need to be re-examined. We believe that they do occupy an important place throughout the acute, mid and long COVID stage. Preventive measures against the development of long COVID, especially neuro-COVID-19, still await further research and clinical trials with better designs.

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