Inflammopharmacology
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REVIEW

Unraveling the enigma of long COVID: novel aspects in pathogenesis, diagnosis, and treatment protocols

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Abstract

Long COVID, now unmistakably identified as a syndromic entity encompassing a complex spectrum of symptoms, demands immediate resolution of its elusive pathogenic underpinnings. The intricate interplay of diverse factors presents a complex puzzle, difficult to resolve, and thus poses a substantial challenge. As instances of long COVID manifest by repeated infections of SARS-CoV-2 and genetic predisposition, a detailed understanding in this regard is needed. This endeavor is a comprehensive exploration and analysis of the cascading pathogenetic events driven by viral persistence and replication. Beyond its morbidity, long COVID, more disabling than fatal, exacts one of the most substantial tolls on public health in contemporary times, with the potential to cripple national economies. The paper introduces a unified theory of long COVID, detailing a novel pathophysiological framework that interlinks persistent SARS-CoV-2 infection, autoimmunity, and systemic vascular pathology. We posit a model where viral reservoirs, immune dysregulation, and genetic predispositions converge to perpetuate disease. It challenges prevailing hypotheses with new evidence, suggesting innovative diagnostic and therapeutic approaches. The paper aims to shift the paradigm in long COVID research by providing an integrative perspective that encapsulates the multifaceted nature of the condition. We explain the immunological mechanisms, hypercoagulability states, and viral reservoirs in the skull that feed NeuroCOVID in patients with long COVID. Also, this study hints toward a patient approach and how to prioritize treatment sequences in long COVID patients in hospitals and clinics.

Keywords COVID-19 · Long COVID · NeuroCOVID · Autoimmunity · SARS-CoV-2 · Viral Persistence · Multi-System Inflammation · Spike Protein

Introduction

Almost 3.5 years into the pandemic, the scientific community is still gripped by the apprehension of uncovering newly emerging findings caused by SARS-CoV-2 in COVID-19 (Morens and Fauci 2020). The unforeseen long-term post-acute COVID syndrome appeared following the pandemic acute phases, now known as long COVID or post-acute syndrome of SARS-CoV-2 (PASC) (Proal and VanElzakker 2021). Long COVID is a daunting challenge in the understanding of its pathogenesis, clinical presentation, and treatment protocols defined to date (Rando et al. 2021).

Based on our knowledge of the immune response against viruses, it was initially thought that COVID-19 would last for a maximum period of 3–6 weeks. However, acute COVID-19 was quickly recognized as a disease that can progress into a chronic phase, with some symptoms persisting beyond a period of 3 months (Chippa et al. 2023). Additionally, it was observed that new symptoms emerged alongside older, persistent ones, expanding the symptomatic profile of long COVID (Koc et al. 2023). The term 'long COVID' originated from sufferers in public forums, which was later formalized into the more clinical nomenclature, ‘long COVID syndrome’ or ‘PASC’ post-acute sequelae of SARS-CoV-2 infection (Rezkalla and Kloner 2021). Long COVID, as a disease state, began to be acknowledged belatedly, and initially, some in the medical profession considered it to be more of a psychological disorder in patients who had experienced the acute phase, with many still not recognizing

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or understanding the condition (Lemogne et al. 2023). Those studying long COVID recognized that the disease state had a factual basis as indicated by a variety of altered marker profiles observed in many patients (Lai et al. 2023a, b). Long COVID has resulted in more cases of disability than death among patients, emerging as a significant burden on the economies of many developed nations (Forstag and Denning 2022). After the recognition of long COVID as a disease state, the most important question was, and still is, to underpin the basic underlying pathways that form the basis of the disease, the understanding of which is important because it can formulate the basis of a treatment regimen for affected patients. Given the wide range of symptoms associated with long COVID, it is understandable that its pathogenesis is complex and challenging to unravel. Some argue that there may be a single underlying mechanism, for example, ischemia stemming from a hypercoagulable state of the blood, or associated conditions like autoimmunity which in reality are more an effect than the cause of long COVID (Abou-Ismail et al. 2020; Sin 2023). Hypercoagulability and ischemia-related reduction of blood flow to the tissues, when traced back, should logically have a triggering event provoking this pathogenetic mechanism which is discussed in detail in the sections below. Similarly, autoimmune responses require a stimulus, such as an antigenic challenge, to be activated and subsequently produce symptoms (Rojas et al. 2023). Since acute COVID remains the cause that progresses into the prolonged state of long COVID, it is logical to conclude that patients do carry something from the acute COVID phase into chronicity, as evidenced by numerous recent studies (Lai et al. 2023a, b; Koc et al. 2022; Astin et al. 2023). Samples of blood collected randomly, for example at four different times of the day, three different days of the week, could detect the episodic antigenemia that is postulated here to be the cause of the fluctuating severity of symptoms experienced by patients with long COVID. Such tests, though inconvenient and costly, are the only way by which such a variable viral replication, and therefore antigenemia, can be traced back to a virus that not only persists, but also replicates episodically. Persistence of the virus due to inadequate clearance by the immune system causing continuous cytokine release (Fig. 1) after the acute phase that continues into chronicity is the proposed cause of long COVID. We postulate that a low-grade smoldering inflammatory response secondary to antigenic challenge due to periodic replication of persistent virus is the most likely explanation (Fig. 1) why symptoms are sometimes known to become flared up compared to intervals of lesser replication where patients feel somewhat less symptomatic. An immune response to such variable antigenic challenges from time to time can formulate the basis of the signs and symptoms observed in patients with long COVID. Persistence of a virus from a previous infection of acute COVID does not necessarily mean a constant viral replication in the protracted stage. The virus can conceal itself and cause (see "Persistence of SARS-CoV-2 and its shed proteins as a basis of cascades of events leading to signs and symptoms in long COVID") variable antigenemia by its related proteins contributing to an immune reactivation and cytokine release leading to organ injury and damage in long COVID (Tobler et al. 2022; Bowe et al. 2021). Bringing the above-described antigenemia into context and the consequences that can emerge from proteins detached from the virus, we will show how a unified hypothesis can explain the pathogenetic basis of long COVID.

Persistence of SARS-CoV-2 and its shed proteins as a basis of cascades of events leading to signs and symptoms in long COVID

More important than understanding the covert mechanisms underlying long COVID is the question why only a subfraction of the people who are infected by COVID-19 continue into the protracted phase of long COVID (Astin et al. 2023). This understanding is expected to unravel important clues that form the basis of long COVID syndrome. A challenging aspect in uncovering a unified theory as a basis for long COVID is identifying the factor(s) that patients with long COVID carry from the initial infection into a period beyond the acute phase into chronicity. The HLA genotype of an individual who fails to mount an immune response that completely eradicates the virus (Fig. 1A and B) can enable the virus to seek sites in the human body where it can hide, reside, and replicate as in the case of certain hepatotropic viruses (Baig 2020). There are many other examples of such organ-specific viruses where an incomplete eradication leads to chronic phases with organ injury and failure (Boldogh et al. 1996). In the human body, SARS-CoV-2 can conceal itself to later infect and cause viremia (Chen et al. 2023). Sites such as the human gut (reservoirs like crypts of villi), potential places in the skull like air sinuses, and alveolar spaces are some examples (Chen et al. 2023; Zollner et al. 2022). We propose that invasion of neighboring naive host cells with viral budding at these sites can be a source of many viral proteins that can enter human body fluids such as the blood to challenge the immune system (Fig. 1A), a phenomenon that can be persistent or episodic as described in the introduction. From body cavities that have hollow spaces lined by epithelium, for example frontal, ethmoidal, and mastoid air cells via the middle ear and maxillary air sinuses (Fig. 1B), the resident virus can infect the lining epithelium via ACE2 or non-ACE2-dependent mechanisms causing the cells to sprout virions into the basally located

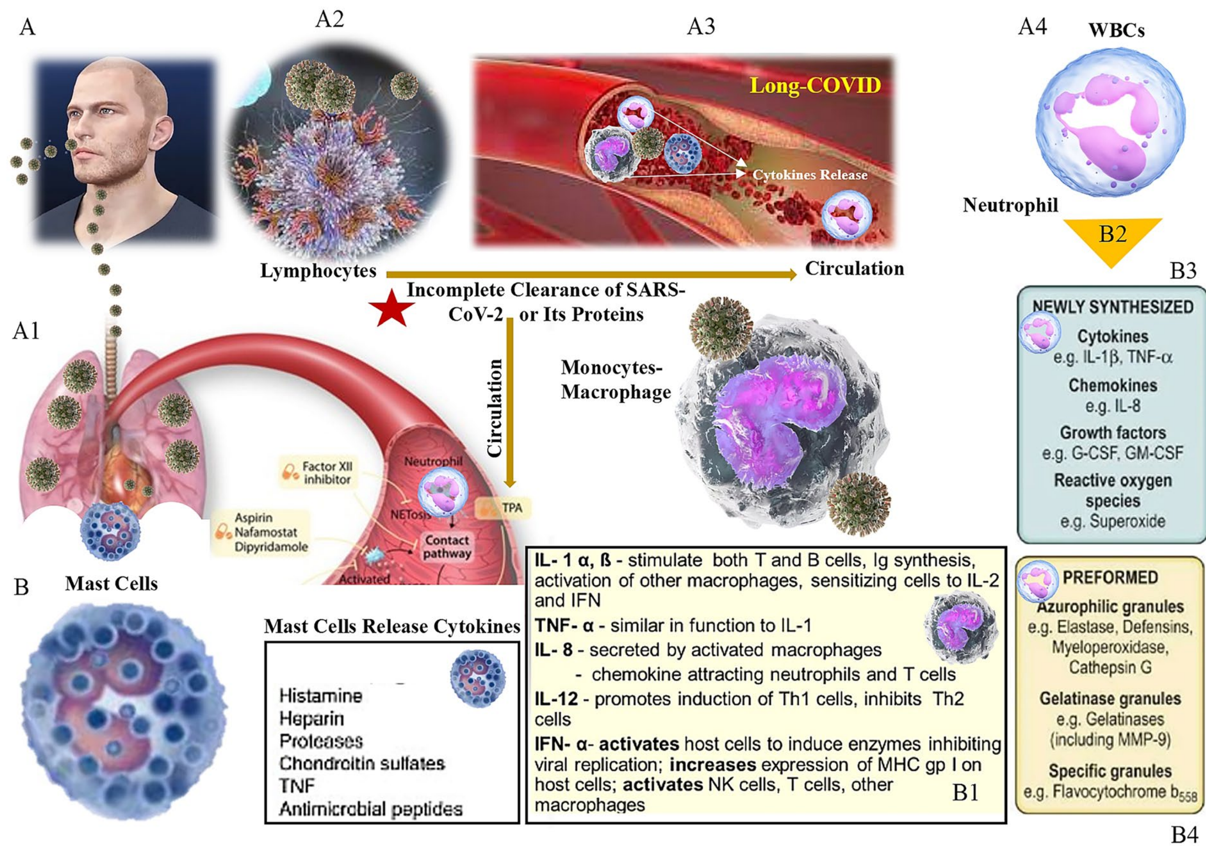

Fig. 1 The events following SARS-CoV-2 infection (**A**) which initially targets the lungs (**A1**—top left to bottom). In a state of long COVID inadequate clearance of the virus by lymphocytes (**A2**—top left to right), the resident virus causes phases of viremia (**A3**—top center), followed by immune system-mediated cytokine release by WBCs (**A4**—top right) and mast cells (**B**—bottom left). The monocyte–macrophage system which uptakes the virus not only serves as their reservoir, but also releases an array of cytokines (**B1**—rectangle below the macrophage image). Other WBCs like neutrophils (**A4**—top right) release a list of cytokines (**B2**—two rectangles below the neutrophil image) resulting in amplification of the immune response. Mast cell activation (**B**—bottom left) leads to the manifestation of allergic response seen in patients with long-term COVID-19

blood vessels. Repetition of this process can be the basis of transient viremia that provokes the immune system to become periodically stimulated. A persistent infection of the gut coupled with the bacteriophage potential of SARS-CoV-2 can lead to the escape of virions into the portal circulation and eventually to the systemic blood flow. The flare-ups and periods of relatively milder symptoms can be explained by the differential grade of the viremia described above for air sinuses, gut spaces, and other cavities that exist in the human body. A method to test this in long COVID is to check the levels of antibodies against the nucleocapsid (N) antigen which reflects viral replication (Haddad et al. 2020). Any level of IgM against N antigen greater than zero would be evidence of viral replication; however, periodic checks are needed as it is difficult to predict the time frame in which the above-described viremia occurs in real time. Reliance therefore should not be placed on the outcome of a single test which could be deceiving.

Determination of IgM and IgG levels against spike protein (S) is also an important adjuvant test that should be done parallel to the IgM tests against the N protein. This is because the IgM and IgG against the S protein could show positivity in a post-vaccinated person. A reinfection should be ruled out by conducting a PCR test in the nose and throat at the time the above two tests are requested, as reinfections can also result in IgM tests against N protein turning positive thereby confusing reinfection with viral persistence-related replication. The theory of viral persistence in long COVID has been challenged and debated from time to time, but there are reports of biopsies and autopsies confirming SARS-CoV-2 RNA in published literature (Stein et al. 2022; Buonsenso et al. 2023). With a majority of symptoms in long COVID resembling acute phase COVID, it is conceivable that an ongoing immunological flare resulting from re-exposure to the viral proteins produced by persisting virus is at play in long COVID (Guzman-Esquivel et al. 2023).

Immunological basis of the signs and symptoms of long COVID

Basic to the understanding of organ injury in long COVID is the concept of diverse pathways by which the immunological response mounted toward SARS-CoV-2 in acute COVID can continue into a protracted course during long COVID coupled with immunological flare-ups caused by viral replication due to its persistence. Below is a summary (Fig. 2) of the cumulative pathways (excluding autoimmunity) that can be elicited by the immune system which can become the basis of the signs and symptoms of long COVID.

An immune response mounted by the humoral immune system against SARS-CoV-2 proteins, specifically the S protein, due to the resident virus in long COVID is capable of inciting the complement system through different types of hypersensitivity reactions (HSRs) (Zheng et al. 2022). Complement activation products such as C3a, C5a, and C5b9 (Fig. 3) can then set up the cascade of cytokine release (Chauhan et al. 2020; Lim et al. 2023). As compared to the cytokine storm in acute phase COVID, the cytokine release in long COVID is of a lesser grade quantitatively and comparatively but is sufficient to evoke the signs and symptoms that are known to be associated with long COVID (Low et al. 2023). The HSRs can drive cytokine production either episodically or in a continuum depending upon the viremia detailed in "Persistence of SARS-CoV-2 and its shed

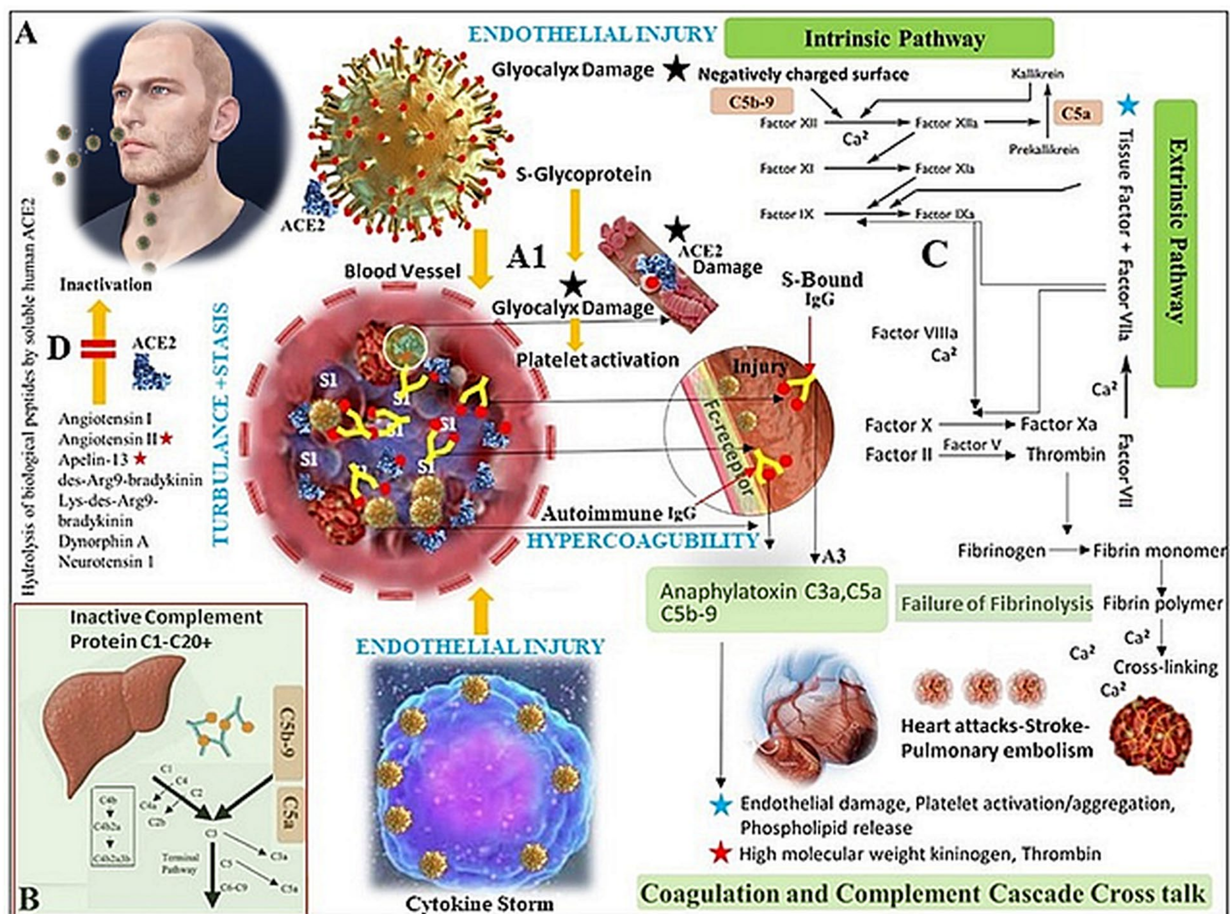

Fig. 2 Following the infection of SARS-CoV-2 (**A**), the S1 component of the spike protein (red dots over the virus—**A1**) shed after the viral entry inside the cell excites the immune system to mount IgGs (Y-shaped yellow structures), which bind to the S1 component of the spike protein and also engage with the Fc portion of the endothelium. The S glycoprotein damages the glycocalyx to reach the endothelium as well (**A1**-rounded red wheel structure). A sequence of events including platelet aggregation and activation of the coagulation pathways (**C**) occur secondary to the endothelial injury resulting in the formation of abnormal platelet aggregates with fibrils enabling the formation of thrombi. Complement factors-driven stimulation (**B**, and brown rectangles at the top right of the figure). Cytokine release by WBCs, autoimmune antibodies, and inadequate clearance of endogenous molecules that maintain a streamlined blood flow also encourages the formation of thrombi (**D**). These thrombi are responsible for incidences of heart attack, stroke, and pulmonary embolism (lower right corner)

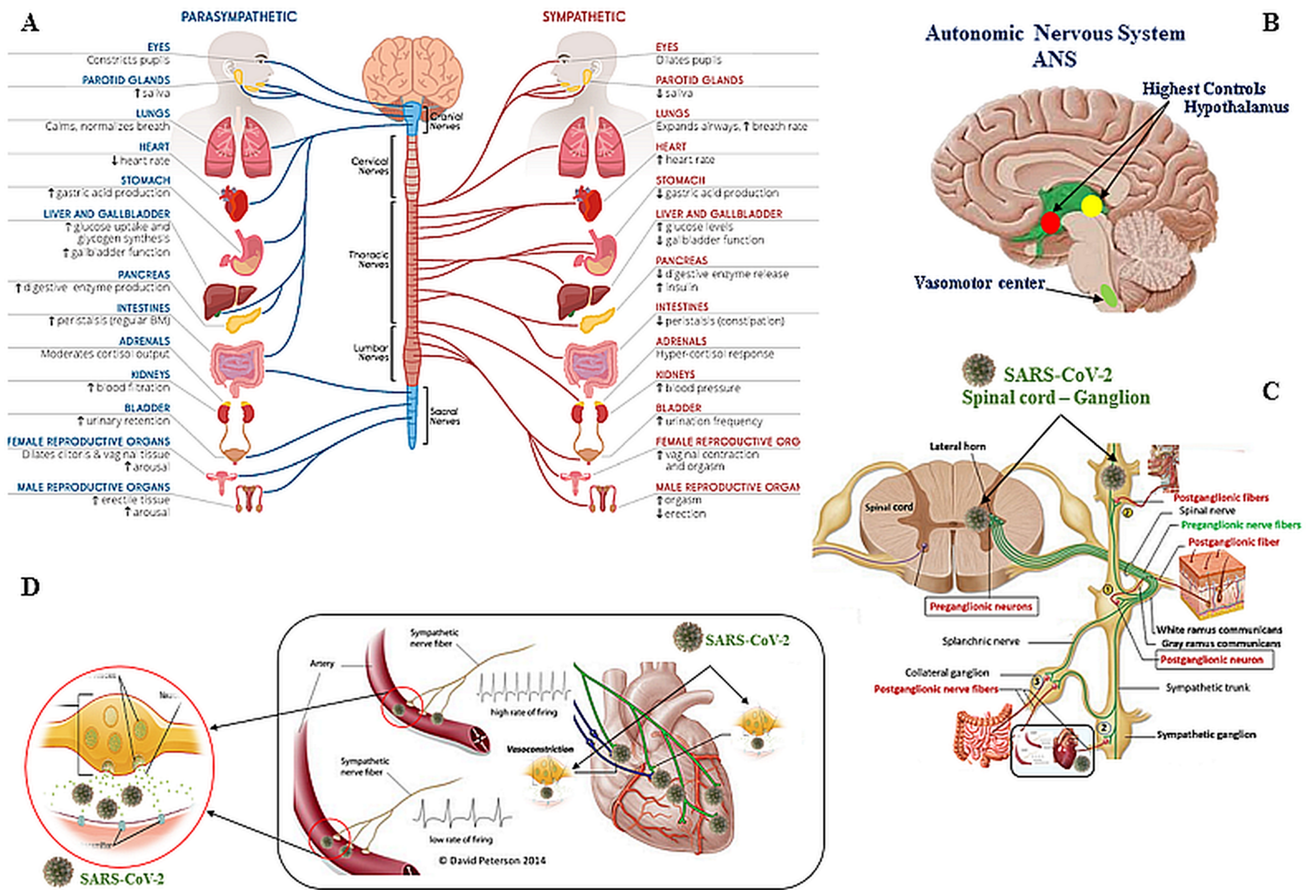

Fig. 3 Dysautonomia seen in long COVID affects the sympathetic and parasympathetic nervous system (**A**) and therefore the functions of organs and systems as shown. The persistent virus in the highest centers of the brain (**B**) can be the cause of this state. Also, the involvement of ganglia and motor neurons (**C**) can induce a dysautonomic state. Demyelination of the nerves of both the systems (**D**) as well as antagonism of neurotransmitters by binding these molecules with SARS-CoV-2 proteins can induce an autonomic paralytic state seen in long COVID. Autoimmune antibodies directed against fragments of S protein (see text) can cross-react with effector organ receptors like muscarinic and adrenergic subtypes, leading to a dysautonomic state as detailed in the sections below. Some organ systems such as adrenal glands can be a dual target of SARS-CoV-2 as well as autoimmune antibodies as evidenced by low cortisol levels in cases of long COVID. The latter also applies to many other organs which show a lower level of functionality (Adapted from https://anatomyqa.com/autonomic-nervous-system-sympathetic-parasympathetic/)

proteins as a basis of cascades of events leading to signs and symptoms in long COVID".

The response of cellular immunity against SARS-CoV-2 and its related proteins can cause organ injury by antibody-dependent cell-mediated cytotoxicity (ADCC) or target cell apoptosis that involves granzyme (Yu et al. 2021; Dizaji Asl et al. 2022). IgG type antibodies engaged with an antigen can incite several non-immune pathways to cause organ injury, of which endothelial damage, activation of the clotting cascade and mast cell activation including white blood cells (WBCs) evoke inflammation and possible damage to components of the nervous system due to the engagement of the Fc portion of IgG with neuronal tissue and glial cells (Sumantri and Rengganis 2023; Arish et al. 2023; Davis et al. 2023). Cells in the kidney, brain, joints, blood vessels, and GIT bear this receptor for the Fc portion of the IgG; therefore, organ-related symptoms are expected in patients with long COVID and are being observed (McConnell and Hurd 1976; Brown 1978; Najafi and Javanmard 2023).

The most concerning aspect of S protein and IgG complexes arises when they circulate freely in the bloodstream. These circulating immune complexes can not only lodge in organs and tissues, but also activate the complement system within the circulatory system (Lim et al. 2023; Ankerhold et al. 2022). This may lead to indirect endothelial injury, which triggers the coagulation cascade and promote aggressive platelet aggregation at the injury site, with or without the activation of clotting proteins (Kumar et al. 2023; Higashikuni et al. 2021). Inevitably, such aggregation within the microcirculation could lead to tissue ischemia, resulting in symptoms of hypoxia in the affected organs and systems leading to the plethora of signs

and symptoms experienced by patients with long COVID (Turner et al. 2023).

One of the worrying aspects of the effects of SARS-CoV-2 in COVID-19 in both the acute phase and long COVID is the ability of this virus to infect and cause both quantitative and qualitative lymphocytopenia (Rahimmanesh et al. 2022; Gerlach et al. 2023). The qualitative type is a state in which the count of the immune-regulating cells may appear to be normal, but are functionally crippled to mount an immune response (2022; Gerlach et al. 2023). In this case when presented with an antigen, the lymphocyte either has a problem with recognition of the antigen or with the cascade that normally follows such antigen presentation. Such a state is of grave concern as it not only increases the chances of the virus to persist, but also predisposes to opportunistic infections and re-emergence of other persisting viruses such as EBV (Walker and Warnatz 2006; Panackal et al. 2017). With the emerging data, this concern is becoming highlighted and is expected to burden the healthcare system now and in the near future (Menges et al. 2021).

Autoimmune antibodies as a cause of signs and symptoms in long COVID

An array of anti-GPCR antibodies is reported in long COVID patients and are considered to be the basis of many of their symptoms (Wallukat et al. 2021). The molecular basis of these autoantibodies is discussed in the sections below where we will also put forward the relevant syndromic manifestations of these anti-GPCR antibodies. Several types of autoantibodies have been reported in individuals with COVID-19 and long COVID. These include:

1. Anti-nuclear/extractable-nuclear antibodies (ANAs/ENAs), which were found to persist up to a year after infection and were associated with the development of post-acute sequelae of COVID-19 (PASC) symptoms such as fatigue, cough, and dyspnea (Son et al. 2023; Larionova et al. 2022). A lupus-like picture can emerge due to ANAs (Butt et al. 2022).
2. Functionally active autoantibodies against G-protein-coupled receptors (GPCR-AAbs), which were observed in patients post-SARS-CoV-2 infection and might be linked to an impaired retinal capillary microcirculation, potentially reflecting systemic microcirculation issues and consecutive clinical symptoms (Wallukat et al. 2021). Several of these GPCR-AAbs are detailed below which are not necessarily directly involved, but can elicit organ injury by indirect mechanisms leading to symptoms.
3. Anti-phospholipid autoantibodies, which are involved in the control of blood clotting, were found in a significant proportion of hospitalized COVID-19 patients (Butt et al. 2022).
4. Autoantibodies neutralizing high concentrations of type I interferons (IFNs), which were identified in ICU patients and associated with a higher risk of severe disease and mortality (Solanich et al. 2021).
5. Anti-annexin A2 autoantibodies, which are associated with increased systemic thrombosis, cell death, and non-cardiogenic pulmonary edema, and may predict mortality in hospitalized COVID-19 patients (Zuniga et al. 2021).
6. Especially in connection with long COVID, there are reports of GPCR-AAbs against muscarinic, alpha-adrenergic, and beta-adrenergic receptors explaining many symptoms related to dysautonomia observed in these patients.

These GPCR-AAbs can either block or damage the receptors they target resulting in signs and symptoms. For example, GPCR-AAbs against the alpha 1 adrenergic receptor can cause POTS (Fig. 3) by preventing vasoconstriction that occurs as a reflex on attaining an erect posture from a lying position. Systemic hypotension with symptoms of dizziness can result from these autoantibodies as well. GPCR-AAbs against the beta 1 adrenergic receptor (Fig. 3) can cause decreased myocardial contractibility and bradycardia which may cause related symptoms like hypotension and palpitations. GPCR-AAbs against the muscarinic receptor can affect smooth muscle contraction, glandular secretions, neuronal function, cardiac rhythm and conduction, and the function of adrenal medulla and autonomic ganglia which enable physiological day-to-day function of these organs. Gut motility in particular is seen to be affected by muscarinic type 3 receptors (M3), which can be linked to constipation and paralytic ileus reported in many long COVID patients. Autoantibodies against M1 and M3 receptors on neuronal tissue provide a possible explanation for the cognitive deficits, memory loss, and brain fog experienced by almost all patients in long COVID.

Possible mechanisms involving endothelial injury and hypercoagulability in long COVID at the molecular level

Although more an effect than a cause of long COVID, endothelial injury and hypercoagulability leading to the formation of abnormal platelet aggregates, misdesignated as “microclots”, has gained considerable attention because of the transient relief reported after sessions of HELP apheresis and anticoagulant drugs (Higashikuni et al. 2021; Turner et al. 2023; Jaeger et al. 2022). Early during the pandemic when patients started being admitted to hospital, it was

discovered that the majority had ischemic complications related to hypercoagulable blood (Zhang et al. 2021). After the acute phase was over, many patients continued to exhibit abnormal platelet aggregates and elongated fibril-like proteins that were termed "microclots" which is a misnomer, as being intravascular structures, they either should have the term 'thrombi' or 'abnormal platelet aggregates' (Duchareme 2022). Even designating them the term thrombi is conceptually wrong, as such masses were never reported to cause infarction by becoming emboli or to cause partial or complete obstruction of the blood vessels. The term "clot", micro or macro, again would be incorrect, as a clot is an extravascular mass formed from the constituents of the blood that include not only aggregated platelets, but also coagulation factors. Additionally, the formation of a clot is a physiological phenomenon following injury to a blood vessel that causes it to bleed (Barrett et al. 2019). When viewed under a fluorescent microscope, aggressive, enlarged platelets with surface projections were observed along with elongated fibers which are possibly fibrinogen or fibrin-like threads, on which a compositional analysis remains to be done (Jaeger et al. 2022). These fibers are now termed amyloidogenic fibrils, but their exact composition remains unknown.

The role of S protein in the hypercoagulable state and related tissue hypoperfusion in COVID-19 and long COVID is pivotal. It is important to note that there is more than one mechanism by which the S protein can cause tissue ischemia and resultant hypoxia (Haidar et al. 2022). Summarized below are the diverse ways in which the S protein can ignite organ injury by inducing a state of coagulopathy resulting in tissue ischemia secondary to hypoxia also summarized in Fig. 2.

1. ACE2-dependent S protein-mediated endothelial injury.
2. Non-ACE2-mediated endothelial injury.
3. S protein-driven coagulopathy independent of platelet contribution.
4. S protein—IgG complex mediated complement activation leading to endothelial injury and clotting factor activation.
5. Amyloidogenic proteins or peptides derived from S protein causing abnormal platelet aggregation and activation of the coagulation cascade in microcirculation leading to ischemia.

In addition to the activation of platelets and the coagulation cascade, deficiencies of anticlotting agents have been reported for COVID-19, with protein C being an example (Elshafie et al. 2023). It would not be surprising if the inciting events that lead to deficiency of these factors continue into long COVID as it would elucidate the concept of long COVID being a post-acute COVID-19 sequelae (PASC). The following problems with the anticoagulant and fibrinolytic system have been reported for COVID-19 and long COVID:

Anticoagulant system abnormalities

- *Protein C and Protein S deficiency*: Deficiencies in Protein C and Protein S, which are vital for regulating the coagulation cascade, have been observed (Gupta and Patibandla 2023). These deficiencies can lead to deactivation of factors Va and VIIIa, increasing the risk of clot formation (Gupta and Patibandla 2023).
- *Antithrombin (AT) deficiency*: Studies have reported reduced levels of antithrombin in severe COVID-19 cases, which can contribute to a hypercoagulable state (Joshi et al. 2021).
- *Endothelial dysfunction*: COVID-19 can lead to endothelial injury and dysfunction, which in turn reduces the production of anticoagulant factors such as heparan sulfate and increases the expression of procoagulant elements as tissue factors (Higashikuni et al. 2021; Kinaneh et al. 2021).

Fibrinolytic system alterations

- *Elevated plasminogen activator inhibitor-1 (PAI-1)*: Increased levels of PAI-1 have been noted in COVID-19 patients, which can inhibit fibrinolysis and contribute to thrombosis (Whyte et al. 2022).
- *Reduced tissue plasminogen activator (tPA) activity*: Although tPA levels might be elevated as an acute phase reactant, its activity could be inhibited by increased PAI-1 levels (Urano et al. 2019).

Thrombin generation and fibrinolysis

- *Elevated D-dimer levels*: A common finding in COVID-19 patients, elevated D-dimer levels indicate increased thrombin generation and fibrinolysis (Gerber and Chaturvedi 2021). This is often a marker of a prothrombotic state and can be used to assess the severity of the disease and the risk of thrombotic complications (Gerber and Chaturvedi 2021).

One of the daunting tasks in long COVID is to answer the question of why these abnormal platelet aggregates coupled with amyloidogenic fibrils are difficult to lyse by the fibrinolytic system of the body (Kell et al. 2022). One possible explanation for the above question is that these platelet aggregates with the fibrils are not the substrate of well-known agents belonging to the physiological fibrinolytic system. The intrinsic fibrinolytic system and the therapeutic approach to lyse thrombi have known

substrates that are made up of constituents that can be lysed by these approaches. Given the presence of amyloidogenic components and some yet unknown components of the thrombi found in long COVID, it is resistant to lytic process by known processes.

Pathological basis of neurological deficits as pivotal disability featuring in long COVID

NeuroCOVID in long COVID has been observed to predominate in patients presenting in clinics and hospitals (Baig and Gerlach 2023). A feature unique to the nervous system, particularly the brain, is that it can become infected by SARS-CoV-2 early in the course of COVID-19 via viral access through the cribriform plate located at the upper part of the nose (Baig and Gerlach 2023). With the nose being the principal site of viral load, this route of infection has been elucidated by many studies in published literature (Zou et al. 2020; Ylikoski et al. 2020). Unlike the concept of residual virus presented in this paper, this route is more ominous than previously thought. The pits of the cribriform plate and areas beneath the olfactory bulb including potential spaces such as the air sinuses can be a reservoir for not only viral persistence, but also its replication. Though the hematological spread of SARS-CoV-2 to the brain has also been documented in the context of COVID-19 with viral persistence driving chronic infection, the upper part of the nose and the structures surrounding it appear to be ideal sites for access to the CNS (Baig et al. 2020). The finding of SARS-CoV-2 mRNA within the openings of the cribriform plate and the structures surrounding it (Meinhardt et al. 2021) confirms that reservoirs at these areas are viable sites harboring the virus. This can cause a low-grade inflammation in the meninges and deeper tissues in the neuronal environment triggering neuroinflammation which becomes the basis of brain fog. Symptoms such as brain fog, cognitive deficits, prolonged anosmia, memory deficits, and deposition of amyloid-like fibrils that cause premature aging are observed in patients with long COVID. Cells responsible for production of myelin sheath over axons (Patel et al. 2022) when targeted can result in demyelination and its resulting consequences, which could be the basis of sensorimotor deficits seen in patients with long COVID (Fig. 4).

Convergence point of pathogenic events underlying long COVID

Central to the understanding of the spectrum of disease symptoms in long COVID is the concept that the persistence of the immune complex and cytokine pathways is secondary to the challenge imposed by viral persistence. All the symptom complexes discussed above converge onto a single event that drives multiple inflammatory pathways to induce organ injury, leading to the syndromic picture the patients present. As discussed above, even in the face of a negative test for viral persistence or the presence of proteins shed by SARS-CoV-2, viral hideouts in places where blood vessels do not have access should be thoroughly searched and sampled for presence of the virus.

Many known pathogenic events in long COVID which are considered to dominate the syndromic scenario are more an effect rather than the cause.

Organs and systems affected in long COVID; priority-based treatment protocol for patients with long COVID

It is important to note that despite the signs and symptoms of long COVID being diverse and complex, the majority of patients present with a single organ-related cause which needs to be carefully considered for the determination of a treatment protocol. One example is a patient presenting with hypomotility of the gut coupled with a decrease in skeletal muscle tone and power as well as visual disturbances and vertigo. In-depth correlation and investigation are needed to ascribe these features as symptoms of NeuroCOVID though at a glance it appears to be GIT dysbiosis, musculoskeletal, ocular, and issues related to internal ear disturbances respectively. The related neural dysfunction namely vagus nerve defects, somatic motor nerve demyelination, optic neuropathy, and neuropathies involving the VIII cranial nerve or its ganglion are all features of NeuroCOVID. In other instances, a mixed picture of organ dysfunction emerges which classifies them into a mixed variant of long COVID. Figure 5 shows how to approach patients with long COVID and ascribe them to a particular group which helps determine the type of therapy suitable for a particular patient. The art of clinical practice in long COVID is to converge the relevant symptoms and seek an explanation of the presenting complaints.

Long COVID: pharmacology of drugs and supplements of potential benefits

Reviewing the potential benefits of drugs and supplements in the management of long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), involves understanding the complex and varied symptomatology of the condition. As long COVID encompasses a wide range of symptoms and systems affected, treatments are often aimed at addressing specific symptoms rather than the condition as a whole. This review will delve into several categories,

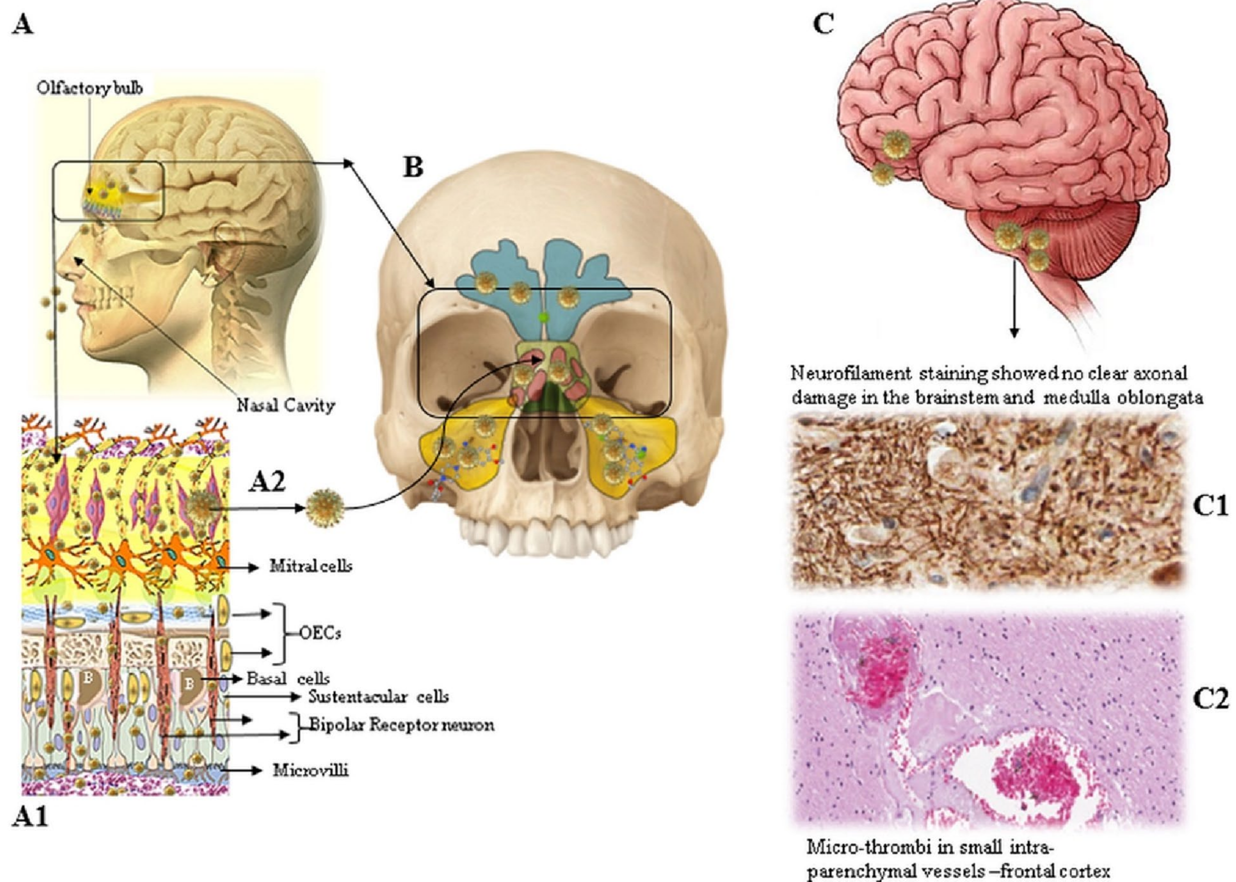

Fig. 4 The viral reservoirs in the skull that can serve the brain with SARS-CoV-2 causing neurological symptoms in long COVID. The cribriform plate fossa (**A**, **B**), adjoining parts of the olfactory mucosa (**A1**, **A2**), and air sinuses (**B**) with their hollow cavities are known to contain the virus, and reports of SARS-CoV-2 mRNA have been published about areas such as the cribriform plate. Brain fog, cognitive deficits, and neuroinflammation can be driven by sustained or periodic viral access to the brain laying the basis of cerebral symptoms in long COVID In the brain (**C**) the SARS-CoV-2 does not causes axonal damage (**C1**) but formation of microthrombi can occur (**C2**), which can develop into neurological signs and symptoms. (B- was adopted from https://quizlet.com/397341840/terminologi-skelettet-flash-cards/?src=set_page_ssr) [C1-C2 Adapted from https://www.mdpi.com/2218-273X/12/5/629]

including immunomodulatory treatments, antiviral agents, supplements, and symptomatic treatments, based on available research and clinical findings up to my last knowledge update in April 2023.

Immunomodulatory treatments

1. *Corticosteroids*: These are often considered for their anti-inflammatory effects. However, their use in long COVID is controversial due to potential side effects and the risk of long-term immunosuppression. Their application might be considered in cases with severe inflammatory markers or specific organ inflammation documented.
2. *Mode of action*: Reduce inflammation through suppression of the immune system's inflammatory pathways.
3. *Efficacy*: Varied; may benefit certain patients with severe inflammatory responses, but not universally effective for all long COVID symptoms.
4. *Safety*: Long-term use can lead to complications like osteoporosis, adrenal suppression, increased infection risk, and more.
5. *Limitations*: Risk of serious side effects and lack of specificity for long COVID-associated inflammation.
6. *Interferons*: Given the role of interferons in viral defense, there is speculation about their utility in managing long COVID, especially for patients with lingering viral reservoirs or reactivation of latent viruses. However, evidence remains anecdotal, and more research is needed.
7. *Mode of action*: Enhance the body's antiviral defenses by modulating the immune response.

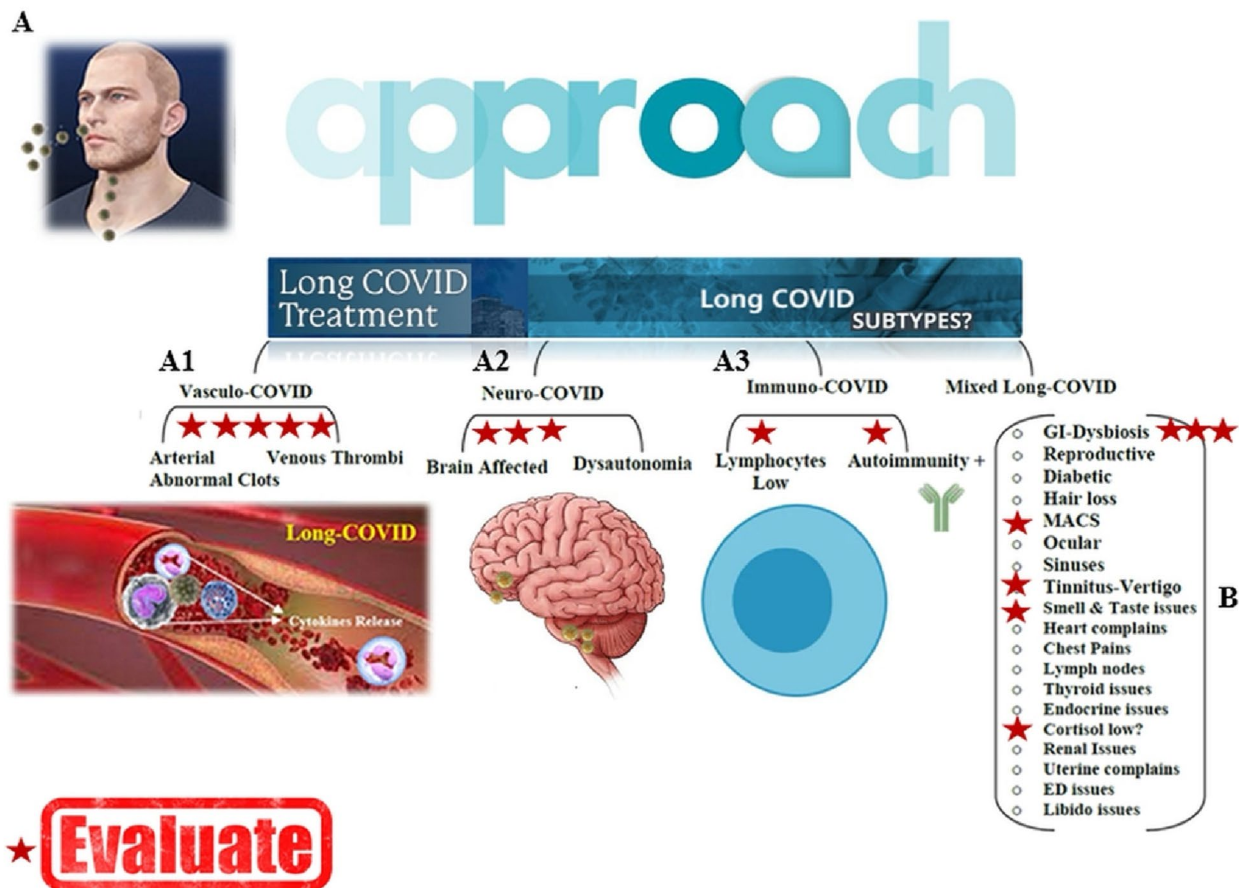

Fig. 5 Schematic representation of approach to a patient with long COVID. The acute infection (**A**) with SARS-CoV-2 leads to long COVID, which presents as complex organ symptoms (**A1**, **A2**, **A3**, **B**). The art of a meaningful evaluation should be based on a scoring system (red stars) with the highest scored organ to be placed at priority as in the above case: vasculo-COVID with five stars, if complaints such as palpitations, ischemia-related organ complaints, blood pressure fluctuations, sinus bradycardia, and conduction abnormalities present as regularly irregular pulse. Though an overlap of the causative organ in question is possible, every attempt should be made to individualize the symptoms to the organ under investigation. In the case of other organs and systems in question, a similar grading mechanism is advised. In cases where the symptoms are diverse, a diagnosis of mixed long COVID should be declared (**B**)

8. *Efficacy*: Uncertain in long COVID; theoretically beneficial, but lacks substantial evidence.
9. *Safety*: Can cause flu-like symptoms, mood changes, and potential liver damage with long-term use.
10. *Limitations*: Limited evidence for effectiveness in long COVID and potential for significant side effects.
11. *Monoclonal antibodies*: Initially used in acute COVID-19 to prevent severe disease, there is interest in understanding their role in long COVID, especially in early treatment phases to mitigate chronic symptoms.
12. *Mode of action*: Target specific components of the immune system or the virus to reduce viral load and modulate inflammation.
13. *Efficacy*: Proven in early treatment of acute COVID-19; efficacy in long COVID is still under investigation.
14. *Safety*: Generally well tolerated, but risks include allergic reactions and potential for immune system impact.
15. *Limitations*: High cost, accessibility issues, and uncertain long-term benefits for long COVID.

Antiviral agents

1. Antivirals: While these have been central in acute COVID-19 treatment, their role in long COVID is less clear. Theoretically, they could help if ongoing viral replication is a factor, but evidence is limited.
2. Ivermectin: Despite its controversial use and lack of support from large-scale studies for acute COVID-19 treatment, some advocate it for its anti-inflammatory

and potential antiviral effects in long COVID. However, medical consensus advises against its use due to insufficient evidence of benefit and concerns over side effects.

Mode of action: Inhibit viral replication, potentially reducing viral persistence.

Efficacy: Established in acute COVID-19; unclear benefit for long COVID due to lack of direct evidence.

Safety: Generally safe with monitored use; side effects include liver enzyme elevations and allergic reactions.

Limitations: Uncertain role in long COVID, requiring intravenous administration and limited by access and cost.

Supplements

1. Vitamin D: There is growing evidence that Vitamin D may play a role in modulating immune responses and potentially mitigating long COVID symptoms. Its role in respiratory health further supports its use, especially in individuals with deficiency.
2. Omega-3 fatty acids: Known for their anti-inflammatory properties, omega-3 supplements could help manage systemic inflammation associated with long COVID.
3. Magnesium and vitamin B complex: These supplements are considered for their roles in energy production and nerve function, potentially addressing fatigue and neurological symptoms in long COVID patients.

Limitations: Overdosages should be avoided as they can cause adverse effects.

Symptomatic treatments

1. Pulmonary rehabilitation: For patients with persistent respiratory symptoms, structured rehabilitation programs can be beneficial.

Experimental approaches

1. Peptide therapy: Targeting specific pathways involved in inflammation and tissue repair, peptide therapy is an experimental approach that has gained attention but requires further research.
2. Stem cell therapy: While highly experimental and not widely recommended, stem cell therapy aims to regenerate damaged tissues, including lung tissue.

The management of long COVID is highly individualized, focusing on specific symptoms experienced by the patient. While there is a growing body of research and clinical trials aimed at understanding and treating long COVID, the evidence base for many treatments remains in development. Patients considering any drugs or supplements should do so under the guidance of a healthcare professional, ensuring treatments are tailored to their specific needs and medical history.

As new research emerges, it is crucial for both patients and clinicians to stay informed about the latest findings and treatment modalities. Collaboration between different specialties is also essential in managing the multifaceted challenges presented by long COVID.

The efficacy, safety, and limitations of peptide therapy and stem cell therapy in long COVID are not well defined due to their experimental nature. Their modes of action are theoretically based on modulating immune responses and repairing damaged tissues, but these treatments require further clinical trials to establish their roles clearly.

In summary, while there are various treatment approaches available for managing long COVID, their application must be individualized, considering the specific symptoms, patient health status, and emerging research. The balance between potential benefits and risks is crucial, emphasizing the need for guidance from healthcare professionals in navigating treatment options.

Discussion and conclusions

Here, a comprehensive unifying description of long COVID is presented. The explanations detailing the basic underlying cause are presented to debate various theories that have been put forward for long COVID in the past 3 years. The persistence of immunologically mediated organ injury secondary to viral persistence and replication drives a low-grade smoldering inflammatory response that we propose to be the basis of long-term COVID-19 symptoms. The possible mechanisms by which residing virus uses ACE2 or other receptor subtypes from hollow cavities that enter into the bloodstream and evoke an immune response are coined and debated here. The heterogeneity of HLA-driven human immune responses is particularly evident in cases where individuals are unable to clear the virus after an initial COVID-19 infection. The inability to eradicate the virus is proposed as a fundamental mechanism for viral persistence and is a novel concept that has been identified as a pathogenetic basis of long COVID here. A particular HLA gene configuration inherited by an individual appears to be the factor at play (Baig 2020). This can be elucidated through large cohort studies by investigating as to which specific gene subsets belonging to the HLA genotype predisposes individuals to long COVID. However, regardless of HLA genotype predisposing to long COVID, repeated infections causing quantitative or qualitative lymphocytopenia (Baig 2020) would make individuals incapable of viral clearance and therefore increase the chance of long COVID. This

acquired qualitative or quantitative lymphocytopenia understandably could predispose individuals to all types of bacterial, fungal, parasitic, or viral infections as seen for example in the well-known cases in India where many oral cavity fungal infections were observed during the early outbreak of COVID-19 in 2020. A similar non-ACE2-mediated uptake of SARS-CoV-2 in immune-regulating cells particularly lymphocytes in long COVID logically would have similar consequences.

The viral proteins, especially the S protein that is shed periodically or persistently in some cases due to viral persistence and replication, amplify the syndromic picture in long COVID. The S protein itself can initiate an uptake mechanism by the ACE2-expressing cells of the body leading to accumulation and subsequent enzymatic digestion within the lysosomal granules, a phenomenon now believed to cause deposition of amyloid beta resulting in hypoxia (Priemer et al. 2022). The action of different leukocytic enzymes, neutrophil elastase in particular (Azevedo et al. 2012; Nyström and Hammarström 2022), has been reported to generate such fibrils in extracellular spaces such as blood vessels, and the neuronal environment. The significance of the effects of COVID-19 on cerebral gray matter leading to its shrinkage has been reported, and continual virus-induced neuroinflammation in long COVID is a popular theory behind NeuroCOVID reported in these patients (Douaud et al. 2022). Here for the first time, the cribriform plate and surrounding areas in the anterior cranial fossa have been proposed as a site of viral reservoir enabling its continuous access to the brain leading to features of NeuroCOVID in this group of patients. We also for the first time show the handshake between complement proteins and the coagulation cascade that occurs with products such as C3a, C5a, and C5b9. A forgotten piece of the puzzle called the glycocalyx which lines the endothelium and normally repels the anionic-charged formed elements of the blood (Reitsma et al. 2007), has been proposed to be the first barrier overcome by the S protein alone and the S protein—IgG complex. The expression of the Fc portion of the endothelium (Pan et al. 1999) driven by inflammation and its engagement of the S protein–IgG complex is proposed to be one of the first driving forces of endothelial damage. We also put forward a way to test levels of antibody against the nucleocapsid (N) antigen (Haddad et al. 2020) which reflects viral replication in long COVID and recommend that a periodic check of this test would be needed as it is difficult to predict the times when viremia from persistent virus would occur. Reliance on the outcome of a single test could be deceiving as it could occur during a quiet period when viral replication is not active or has not yet spilled into the bloodstream.

Unique in the findings that we present here are ways in which GPCR-AAbs can either mask or injure the receptors they target resulting in signs and symptoms of long COVID. Citing one of a few examples we explain POTS that can be a GPCR-AAbs mediated against the alpha 1 adrenergic receptor. Systemic hypotension with symptoms of dizziness can result from these autoantibodies as well. Another example is GPCR-AAbs against the beta 1 adrenergic receptor which can cause decreased myocardial contractibility and bradycardia which may cause related symptoms like hypotension and palpitations. Likewise, explanations provided for muscarinic receptors can affect smooth muscle contraction, glandular secretions, neuronal function, cardiac rhythm and conduction, and function of autonomic ganglia which normally enable day-to-day function of these organs that can be due to GPCR-AAbs against the muscarinic receptor subtypes. Autoantibodies against the M1 and M3 receptors on neuronal tissue have been detailed to provide a possible explanation of the cognitive deficits, memory loss, and brain fog experienced by almost all patients in long COVID. The vagus nerve dysfunction in long COVID can result from widespread GPCR-AAbs against several muscarinic receptor subtypes. Vagus nerve stimulation has been proposed as a treatment modality (Sant'Anna et al. 2023) with short-lived, variable outcomes. The autoantibodies against muscarinic subtype receptors are combated by an excess release of acetylcholine (ACh) on vagus nerve stimulation which explains the transient relief observed by this maneuver.

One of the most important components of this study is to clarify the concept of microclots, microthrombi, and abnormal platelet aggregates. We debate here that the nomenclature of microclot now used widely in literature and the media (Duchareme 2022) to refer to coagulation anomalies in COVID and long COVID is a misnomer and scientifically incorrect. The reasons for this have been outlined above but in summary, a clot, whether micro or macro is a physiological rather than a pathological term and in the absence of ischemia or an infarction as evidence for these solid masses the term cannot be assigned to abnormal platelet aggregates with or without clotting factors like fibrinogen or fibrin. The same applies to the term thrombi. Masses of abnormal platelet aggregates with amyloidogenic fibrils need a new term and should not be confused with the term microclots.

Our study has also highlighted newer sites for virus persistence that serve as a reservoir (Fig. 1). Areas like the cribriform plate and anterior cranial fossa are described in this context in the sections above. Hollow cavities like air sinuses and the gut have been discussed in detail. Immune-evading zones like testicular cells and the neuronal environment across the blood–brain barrier need to be considered as additional possible sites for viral reservoirs. In conclusion, our study has attempted to cover all aspects of long COVID with a rational explanation that is expected

to add to the knowledge of long COVID pathogenesis and help design therapeutic strategies to address the sites of viral reservoir, NeuroCOVID progression, immune system-mediated organ injury, targeting SARS-CoV-2 in body cavities as well as remedies for coagulation activation and endothelial injury.

Future direction

Research into the pathogenetic mechanisms underlying long COVID that are detailed in this study needs to be validated by several investigative tools that can speed up the development of treatment protocols for patients with long COVID. Particularly, routes of administration that can reach the hollow cavities (Baig and Gerlach 2023) and exert virucidal effects urgently need to be implemented. Treatments that can filter out autoantibodies and IgGs bound to the S protein, or the S protein alone such as H.E.L.P. apheresis with or without anticoagulants can produce remarkable clinical efficacy (Jaeger et al. 2022), as these pathogenic factors are pivotal in causing organ injuries in long COVID. Selective molecules that can bind the S protein in SARS-CoV-2 given alone and in combination (Vedicinals 2020) that have shown efficacy in COVID-19 in long COVID can be implemented. Selective removal of AAbs has been attempted but has been reported to remove other antibodies needed for the maintenance of health and protection against infections in general. Also, as newer symptoms are emerging in long COVID, there is a need to use a correct nomenclature for intravascular processes like thrombosis leading to thrombi, instead of referring to intravascular masses as "microclots" circulating in blood, as the latter are part of the physiological process following damage to a blood vessel leading to bleeding. We are optimistic that novel pathways and concepts presented in this paper will prove to be a step forward in our fight against long COVID, which now is without a doubt the most significant disabling disease in modern times. Funding for research and treatment discovery for long COVID are the essential call of the times and any delays in this are guaranteed to produce further disabilities and deaths shortly.

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Declarations

Conflict of interest The authors have not disclosed any competing interests.

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