Summary of a 24-page Paper on Long COVID and the Similarities with ME/CFS

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"Long COVID: pathophysiological factors and abnormalities of coagulation"

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Note:

1. Although this paper is about Long COVID, the authors make it clear that ***"50% of people with Long COVID meet the criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)"*** and there are references to ME/CFS throughout the paper.

2. In view of the stated similarities of the two diseases, the scientific evidence contained in the above paper comprehensively demolishes the long-held beliefs (extensively published as "evidence-based" actuality) of certain UK psychiatrists, including Regius Professor Sir Simon Wessely, Professor Emeritus Peter D. White (lately of St Bartholomew's Hospital London) and Professor Michael Sharpe (lately of the University of Oxford) that ME/CFS is psychosomatic in origin. More recently, Professor Michael Sharpe and his colleague Trudie Chalder are amongst those who are trying to claim not only ME/CFS but now also Long COVID as their own territory (1,2,3,4).

GENERAL INTRODUCTION

The paper sheds light on the various pathological factors that contribute to Long COVID: it highlights the resultant blood abnormalities and it summarises findings that point to a failed fibrinolytic system.

It examines the prevalence and manifestations, the risk factors (emerging evidence suggests that people with pre-existing immune issues are more susceptible to Long COVID) and it defines subtypes of Long COVID. It also discusses the effects of vaccination in relation to Long COVID, noting the inconsistent results and highlighting that COVID 19 vaccination can result in significant adverse effects.

The disease affects about 65 million people worldwide. Common symptoms are multi-systemic and include profound fatigue, breathlessness, cough, chest pain, palpitations, headache, joint pain, myalgia, weakness, insomnia, pins and needles, hair loss, impaired balance, digestive and urinary tract issues, skin rashes and cognitive dysfunction including memory and concentration problems, anxiety and depression. A key symptom is post-exertional symptom exacerbation: many patients struggle to do basic daily activities. Complications include coagulopathy, thromboembolism, multi-organ failure, septic shock and death.

Children of all ages can develop Long COVID and they experience the full range of symptoms seen in adults; additionally, notable manifestations in children include brain hypometabolism, hepatic involvement, ME/CFS and pulmonary abnormalities.

The many pathological processes involved include (i) viral factors (persistence, reactivation, and bacteriophagic action); (ii) host factors (chronic inflammation, metabolic and endocrine dysregulation, immune dysregulation and autoimmunity) and (iii) downstream damage (tissue damage, tissue hypoxia, host dysbiosis and autonomic nervous system dysfunction ie. dysautonomia). These disrupted mechanisms culminate in the long-term persistence of the disorder, which is characterised by endothelial dysfunction (thrombotic endotheliali tis, endothelial inflammation, hyper-activated platelets and fibrinaloid microclots). These abnormalities of blood vessels and coagulation affect every organ system and represent a unifying pathway for the multi-systemic symptoms.

The need for accurate subtyping

The authors are clear that: *"One of the first distinctions that clinicians and researchers evaluating patients with Long COVID must establish is whether the symptoms can be linked to organ dysfunction…(and if so), it is possible that (the patient) will have a positive response to traditional pulmonary rehabilitation efforts. By contrast, a patent who experienced less severe illness (but who) goes on to develop extreme fatigue, shortness of breath, chest pain and exertional intolerance (but whose) mainstream clinical investigations return normal and do not correlate with symptom severity…in these cases, as we have learned from other postviral illnesses, such as ME/CFS, interventions including pulmonary rehabilitation are likely to significantly worsen symptoms".*

The authors name two main categories of Long COVID:

Non-syndromic Long COVID where patients exhibit mainstream test results that correlate with presenting symptoms such as acute kidney failure, pulmonary fibrosis and cardiac pathology.

Syndromic Long COVID where patients present with mainstream test results that do not correlate with presenting symptoms; such presentations include ME/CFS; post-exertional symptom exacerbation (PESE); dysautonomia and autoimmunity.

Pre-existing complex chronic illnesses known to be worsened by COVID: these are listed as ME/CFS; mast cell activation syndrome (MCAS); dysautonomia; Ehlers Danlos syndrome; Lyme disease; Hashimoto's disease; multiple sclerosis and Sjogren's syndrome, all of which the authors emphasise may be worsened by traditional interventional approaches.

The authors emphasise the pressing need to identify the subtypes of Long COVID, stating: *"care must be taken to 'do no harm' by determining whether the patient has the 'syndromic' or 'non-syndromic' subtype of Long COVID, so that individuals with the former are not offered treatment such as graded exercise therapy (GET) or cognitive behavioural therapy (CBT). These treatments have been shown to be harmful and/or ineffective and several guidelines explicitly advise against them".*

DETAILED PATHOPHYSIOLOGY OF LONG COVID

Viral persistence

Viruses can be present in a chronically lytic and/or latent form in the host after the initial phase of infection. There is growing evidence that hidden viral reservoirs may trigger immune responses that contribute to persistent symptoms. The main virulence factor of SARS-Cov-2 is the spike protein, which is a key element for viral attachment to target cells. The S1 subunit permits receptor binding to the host cell, whereas the S2 subunit enables viral fusion and entry. Once inside the host cell, viral replication occurs.

Spike protein can be shed by the host cell itself via extracellular vesicles (EVs); EVs are released by neutrophils, monocytes, lymphocytes, platelets, epithelial cells and endothelial cells. The main function of EVs is to transport cargo (ie. biologically active compounds such as mRNA) to neighbouring or distant cells to support homeostasis. EVs share resemblances with viruses, such as small size and cell entry mechanism. SARS-CoV-2 can hide in EVs and can re-attack distant tissues and organs through the circulatory system.

Reactivation of latent viruses

Dormant viruses may re-activate under conditions of stress or immunosuppression. If the immune response is weakened, challenged or dysregulated, these previously dormant viruses may become active and alter human gene expression, protein production and immune regulation, thereby driving new chronic symptoms.

Bacteriophage-like actions of SARS-Co-V-2

It has recently been suggested that SARS-CoV-2 can infect and replicate in gut bacteria, resulting in a potent type of viral persistence; this may explain the gut dysbiosis seen in patients with Long COVID, further contributing to the chronic inflammation, endothelial dysfunction and hyper-coagulation.

Host factors

Chronic inflammation and immune dysregulation

In response to the virus in acute COVID-19, the immune system stimulates polyclonal T cell activation and the release of inflammatory molecules such as cytokines, interleukins and chemokines (known as a cytokine storm). A cytokine storm is a distinct immunological feature of COVID-19. As the storm intensifies, high levels of inflammatory molecules are increased drastically. It has been shown that severe COVID-19 causes B cell and T cell lymphocyte deficiency (ie. lymphopenia); this in turn can cause hyper-inflammation, because lymphocytes participate in the resolution of inflammation after infection.

Autoimmunity

Bacterial and viral infections have been identified as a key trigger in the pathophysiology of autoimmune diseases. Different mechanisms for the generation of autoimmunity following infections have been proposed. These may include epitope spreading, bystander activation, molecular mimicry and activation of antigen-presenting cells. For instance, Type 1 diabetes mellitus (T1DM) has been associated with coxsackievirus and enteroviruses, whilst hepatitis C virus (HCV) has been postulated to be associated with lupus erythematosus.

Evolving data suggest that autoimmunity contributes to the pathophysiology of SARS-CoV-2 infection, both during the acute phase and in Long COVID: for instance, antiphospholipid autoantibodies have been detected in 52% of serum samples of hospitalised patients and this directly correlates with neutrophil hyper-activity and more severe clinical outcomes.

Mast cell activation

The hyper-inflammatory responses in both acute COVID-19 infection and in Long COVID are thought to be facilitated by mast cell activation. Mast cell activation can escalate into mast cell activation syndrome (MCAS), which causes repeated severe allergic symptoms affecting numerous bodily systems, including food allergies, urticaria, gastrointestinal upset, shortness of breath and wheezing, all of which are reported in Long COVID. The proposed mechanisms include dysregulation of genes by SARS-CoV-2, resulting in the loss of genetic regulation of mast cells, as well as development of autoantibodies which react with immunoglobulin receptors on mast cells.

Melatonin deficiency

Melatonin subdues an overactive innate immune response, thereby downplaying inflammation. It also endorses the adaptive immune reaction, resulting in enhanced antibody formation, thereby limiting the entrance of viruses into cells and limiting their replication. It has been demonstrated that in acute SARS-CoV-2 infection, patients with higher levels of melatonin had lower mortality (so) if a patient had melatonin deficiency, they may be at increased risk of developing Long COVID.

Connective tissue abnormalities

Various autoantibodies have been found in the systemic circulation of patients with Long COVID and connective tissue disorders such as arthritis, lupus and myositis have been reported after Long COVID. In those with Ehlers-Danlos syndrome, the high levels of inflammation present in Long COVID may result in increased connective tissue laxity which, if left unmitigated, could cause visceroptosis and may manifest, for example, with an ME/CFS-like picture due to cranio-cervical instability.

Downstream impacts

Tissue damage due to initial COVID-19 infection

An unforeseen complication of the virus was the multi-organ impairment that it caused. This included structural and metabolic brain abnormalities, neurological symptoms, cardiac abnormalities, myocardial inflammation indicating cardiac injury (observed in 78% who were discharged from hospital), with radiological abnormalities being observed in the lungs, liver, pancreas, kidneys and spleen.

There is mounting evidence that the organ involvement occurs due to spread of the virus by the oro-systemic route: viruses contained in the mouth may spread to different organs through the blood. It is likely that, once the virus has found its way into the organs, it stimulates microvascular *in situ* thrombosis, leading to multiple clinical features.

Tissue hypoxia

Autopsy results of lungs from deceased COVID-19 patients have shown significant pulmonary vascular changes, extensive endothelial damage and thrombosis. Poor oxygenation of blood passing through the lungs results in systemic arterial hypoxia which can cause tissue hypoxia throughout the body. Under hypoxic conditions, immune cells may be triggered to produce inflammatory cytokines, which may further intensify capillary dysfunction.

In the heart, endothelial dysfunction is associated with endothelial cell swelling in small arterioles, capillaries and venules, as well as scattered necrosis of individual myocytes. In the brain, infection of the microvascular endothelium in the subcortical white matter is associated with microscopic ischaemic and haemorrhagic lesions.

Due to the chronic inflammatory milieu, neutrophils may cause capillary obstruction, which can stall blood flow. This happens because neutrophils are larger in diameter than erythrocytes and the average capillary diameter; when excessively activated, they can obstruct capillary flow. The adhesion of hyper-activated neutrophils to capillaries within the lungs, brain, heart and other organs may contribute to the symptoms seen in Long COVID.

Patients with Long COVID may present with fibrin amyloid microclots that promote hypoxia and impaired oxygen exchange. These microclots can block capillaries, thereby causing tissue hypoxia. If oxygen supplied to aerobic tissue is restricted, and then rapidly restored ('re-perfusion') it may cause severe tissue damage.

As well as biomarkers of ischaemia-reperfusion injury, tissue hypoxia also includes low venous saturation, heart rate variability, oxidative stress, lactate accumulation and poor oxygen transfer. The authors regard the extent and breadth of this evidence as compelling.

SARS-CoV-2 interactions with the host microbiome

Several studies suggest that COVID-19 promotes microbiome dysbiosis that could result in persistent symptoms. Dysbiosis is accompanied by inflammation that can instigate dysfunction and breakdown of gut epithelial linings. This in turn can cause increased epithelial permeability, allowing pathogens to translocate into the blood, where their presence can contribute to a range of systemic inflammatory processes which can result in endothelial damage and hyper-coagulation.

Autonomic nervous system dysfunction

High rates of symptoms consistent with dysautonomia are commonly reported by patients with Long

COVID and are a significant burden for the patient. They include orthostatic intolerance, fatigue, palpitations, cognitive impairment, nausea and temperature dysregulation.

There are multiple causes for dysautonomia in Long COVID; these include:

- Relative hypovolaemia due to failure of peripheral vasoconstriction is a feature of both postural orthostatic tachycardia (POTS) and orthostatic hypotension (OH); this causes reduced stroke volume and cardiac output, resulting in impaired tissue oxygen supply which can result in a compensatory sympathetic overdrive and tachycardia
- Cerebral hypoperfusion: orthostatic intolerance, cerebral hypoperfusion and dysautonomia were present in a series of recent studies of patients with Long COVID regardless of whether they met criteria for POTS or OH. This evidence is consistent with studies of impaired cerebral perfusion in ME/CFS. Reliance on criteria for POTS and OH is likely to miss many cases of dysautonomia in Long COVID
- Small fibre neuropathy (SFN) has been documented in Long COVID and is a recognised cause of dysautonomia in the condition. The authors suggest that SFN in Long COVID results from autoantibodies (which have been previously associated with POTS and OH) or from ischaemia of small fibres due to microclots
- Damage due to direct infection or inflammation: SARS-CoV 2 is known to infect and produce its spike proteins widely in both the peripheral and central nervous system. Persistent infection of the vagus or trigeminal nerves may be a driver of dysautonomia symptoms.

Interaction between systemic inflammation and coagulation

The processes of systemic inflammation and coagulation are interdependent: dysregulation may occur as a result of chronic systemic inflammation and thrombotic complications. If the inflammatory process is not properly resolved, acute inflammation may transition to a chronic state. The coagulation cascade can be activated due to the consequent increase in pro-inflammatory cytokines. In addition, chronic systemic inflammation promotes the suppression of certain anticoagulant mechanisms. In summary, chronic systemic inflammation may alter the haemostatic balance to a pro-thrombotic state.

Dysregulated coagulation may modify and prolong the inflammatory response. Moreover, activated coagulation factors can also provoke an inflammatory response by interacting with immune cells to induce the production of inflammatory cytokines. Platelets are also implicated in the regulation of vascular permeability.

Abnormalities of coagulation in Long COVID

Fibrinaloid microclots

Fibrinaloid microclots have also been reported in ME/CFS; these microclots, along with hyper-activated platelets, are likely to be contributing to the thrombotic and systemic inflammatory manifestations of these diseases.

It has also been demonstrated that the spike protein S1 subunit is a pro-inflammatory inflammagen, suggesting that the spike protein has direct pathological effects without being taken up by cells. The microclots are very resistant to digestion protocols. Numerous inflammatory molecules trapped inside Long COVID microclots have been identified by proteomics, as well as numerous antibodies.

If the coagulopathy during the acute phase of the disease is not adequately treated, the resulting impaired oxygen exchange and tissue hypoxia may linger and this may explain the multi-organ manifestations of Long COVID; persistence of symptoms has now been observed for up to three years.

Dysregulated coagulation due to endothelial damage and dysfunction

Research has shown that endothelial inflammation (ie. endothelialitis) may have long-term consequences for vascular function. The vascular endothelium serves as a central interface between inflammation and coagulation, with a crucial role in the regulation of two systems.

Endothelial cells have been found to undergo apoptosis after initial COVID-19 infection and this directly impairs signalling between intercellular channels and upstream vascular smooth muscle cells.

Endothelial damage and dysfunction are observed in Long COVID and have been shown to be strong correlates of the disease: in acute COVID-19 it has already been established that endothelial dysfunction and impairment of the microcirculation are present.

Elevated inflammatory mediators in Long COVID may cause profound changes in microvascular resistance and capillary haemodynamics. Moreover, platelets can also become hyper-activated due to up-regulation of inflammatory and adhesion molecules.

Autopsy studies have revealed the extensive effects of SARS-CoV-2 infection on endothelial cells and this damage may increase cell permeability; additionally, endothelial cells can also fuel the expression of chemokines on their surface, thus promoting neutrophil recruitment that may contribute to thrombosis.

Dysregulated coagulation due to viral persistence

As mentioned, SARS-CoV-2 may hide in extracellular vesicles (EVs) to re-attack various tissues and organs through the circulatory system. When SARS-CoV-2 binds to endothelial cells and platelets it causes endothelial dysfunction and platelet hyper-activation. Furthermore, endothelial damage causes endothelial cells and platelets to produce various cytokines, resulting in chronic inflammation.

Apart from their important function as transporters, EVs have a vital part in inflammation, coagulation and immune regulation. It has been demonstrated that EV-TF (extracellular vesicle-tissue factor) activity is significantly up-regulated in patients hospitalised with COVID-19.

Within the coagulation cascade, TF provides binding sites for pro-coagulant complexes, leading to the formation of thrombin. Thrombin is the final step in the coagulation cascade, which promotes the conversion of fibrin to fibrinogen, causing blood coagulation.

TF-positive EVs are released into the circulation and this may lead to thrombosis.

Dysregulated coagulation due to autoimmunity

Autoantibodies that promote thrombosis have been recognised as an important factor in Long COVID. Antiphospholipid (APL) antibodies in particular promote thrombosis by activating extracellular vesicles and platelets: APL antibodies can directly cause endothelial damage by binding to receptors on extracellular vesicles. This inhibits nitric oxide synthase (NOS) production, thereby decreasing the production of nitric oxide (NO), which is known for its anti-inflammatory and vasodilatory properties.

The reduction in nitric oxide production may contribute to endothelial damage. Endothelial injury promotes the release of inflammatory cytokines. The disrupted cascade ultimately leads to impaired vascular integrity and increased platelet aggregation, causing hyper-coagulation.

Markers of endothelial activation and damage have been shown to correlate with disease severity in Long COVID.

Dysregulated coagulation due to chronic hypoxia and persistent inflammation

Chronic hypoxia within tissues may promote hyper-coagulation and promote apoptosis of extracellular vesicles, which reduces endothelial anticoagulant properties and vascular permeability. Chronic inflammation in Long COVID can stimulate endothelial cells, platelets and inflammatory cells to produce inflammatory cytokines and pro-coagulant factors. This chain of events can damage the protective function of the vascular endothelium, consequently causing abnormal coagulation.

PRIORITIES

The authors are unequivocal: it is now clear that widespread endothelial inflammation is a key feature of COVID-19 disease. The authors argue that a dominant pathological process driving symptom burden is a thrombotic endotheliali tis. This induces a systemic pro-thrombotic state with the formation of anomalous circulating fibrinaloid microclots and hyper-activated platelets driven by elevated levels of pro-coagulant inflammatory molecules, which interact with each other as well as with platelets and the endothelium.

A study of the electronic health records of 48 million adults across England and Wales, together with an analysis of 11.7 million US Veterans' health records, revealed a significantly increased risk of adverse cardiovascular outcomes, including thrombosis-related diseases such as myocardial infarction, acute coronary syndrome, pulmonary embolism and stroke. The same hazard ratio remained elevated in 'mild' cases and in younger patients with no underlying health issues.

A recent comprehensive review of Long COVID identified several research priorities, including the need to build on existing knowledge from similar conditions such as ME/CFS.

There are currently no validated evidence-based treatments for Long COVID. Given the scale and debilitating nature of the condition, the authors emphasise that there is a pressing need for further research into the pathological mechanisms: high calibre research can and should be accelerated.

For the avoidance of doubt, Long COVID was included on the list of diseases which were accorded priority research status by NHS England. On 9th January 2023 Professor Sir Simon Wessely was appointed to the Board of Directors of NHS England. At the same time, Long COVID was removed from NHS England's list of diseases accorded priority research status.

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