Inquiry into Long COVID and Repeated COVID Infections

A simplified account of the mechanism of Long COVID, and how to reduce risk and improve Long COVID symptoms, and its application in prevention of vaccine reactions based on experience in a Long Covid Clinic.

Summary:

Around 30% of patients after a Covid infection continue to report an array of persistent symptoms after infection, with these changes up to and over 2 years and ongoing in roughly 1 in 8. Commonly reported symptoms range from fatigue and dyspnoea to “brain fog” with ongoing disability and disruption of work, social, and home lives.

The use of mast cell blockade with old medication, anti-histamines, eg *fexofenadine* in combination with an anti-ulcer medication from the 1980’s, *famotidine,* have been proven effective in:

1. Reduced severity of COVID infection when contracted
2. Reduction of Long COVID symptoms, especially fatigue and cognitive impairment

The protocol using Mast Cell blockade was developed after successful decoding of the DNA in Long COVID by a molecular biologist working within our Long COVID Clinic. Working then with available research into Mast Cell blockade and Glymphatic System, and amalgamated with the CIFS/ME research at Griffith University, and with assistance from a Long COVID Task Force comprising concerned specialist colleagues, established in May 2022 at the Gold Coast, make it possible to significantly improve or recover most patients within a 4 to 5 week, if not too badly damaged by the inflammatory and micro-embolic cascades that are typical of a COVID infection, in combination with accepted management protocols.

We wish to share the DNA findings as well as the management protocol.

Major Points about COVID

- Long Covid is not one condition.
- The Covid may continue to be active /reactive months after contact (sustained inflammation for at least 8 months, especially if unvaccinated
- It is a microembolic and inflammatory disease that may also add amyloid to fibrin with increased risk Alzheimers, Parkinsons, and neurodegenerative disorder in infants
- Microemboli are a result of histamine receptor 1 (H1) induced fibrinogen. Increased TLR expression and TLR-mediated platelet activation during COVID -19 appears to enhance vascular and coronary thrombosis
- Microglial activation is the most common brain pathology found in patients who died of COVID-19: 42% are affected, and another 15% have microclots in brain tissue.
- Cytokine-induced central sensitisation (inflammatory activation of glial/microglial cells and neuropathic inflammation) is the key driver of the autonomic and inflammatory instability in POTS and the POTS-type of PACS patients. People with cancer are at a higher risk if they contract COVID.
- It may reactivate earlier problems eg EBV, shingles, HSV and stay in cell nuclei
- It appears to be co-related with aggressive malignancy (thought to be Interferon 1 and Natural Killer (NK) cell dysfunction) -no formal data as yet available, but raises concerns over increased malignancy rate
- There is a poor prognosis in obesity, diabetes, hypertension, and atherosclerosis
- Over 65- 60+% increased cardiovascular or cerebrovascular event in next 12 months

- The risk of cardiovascular disease doubled in people who had two infections, and tripled in those who had been infected three times. The numbers translate into 50 extra cases of heart disease per 1,000 people who've had COVID-19 twice.
- High incidence new diabetes
- All the POTS-type PACS patients have underlying conditions that require investigation and management
- Common problems in Long COVID:
    - Fatigue, brain fog and shortness of breath
    - Over 65- 60+% increased cardiovascular or cerebrovascular event in next 12 months
    - Change in microbiome
    - High incidence diabetes
    - Increased incidence of autoimmune disease
    - Neural sensitisation with autonomic dysfunction, triggering multiple problems including Postural Orthostatic Tachycardia Syndrome (POTS.)
    - Potential for increased malignancy

The simplified mechanism of the COVID disease.

Covid enters the body via ACE2 receptors- triggers the cytokine storm after activation of the mast cells by Toll-Like Receptors, releasing cytokines, which are small proteins involved in cell signalling, as well as other inflammatory products, in particular Interleukins 6 and 8 (or IL-6 and IL-8) and Tissue Necrosis Factor alpha (or TNF). The inflammatory response can lead to lung oedema, fibrosis, inflammation that affects heart, kidneys, liver, brain etc, and micro-thromboses and microemboli.

Once inside the body, the virus interacts with Threat Receptors (Toll-Like Receptors or TLRs) with a resultant inflammatory or “cytokine storm” particularly involving inflammatory chemicals- interleukin-6 (IL-6) and Tissue Necrosis factor-α (TNFα).

The hyperinflammatory cytokine storms cause far more morbidity and mortality than from any direct viral cytotoxicity. With the inflammatory response comes cascades of microemboli in some patients, and some of these with amyloid, better known for its association with Alzheimers disease. The venous emboli are a result of histamine receptor 1 (H1)- induced fibrinogen.

Inflammatory microglial activation by IL-6 and TNFα is the most common brain pathology found in patients who died of COVID-19. This same activation is seen in many other conditions, including CIFS/ME, Fibromyalgia and POTS.

In the immune system, histamine is mainly stored in cytoplasmic granules of mast cells and basophils and is released upon triggering along with other mediators such as serotonin and tryptase. Mast cell histamine is a regulator of proinflammatory, fibrotic, and thrombogenic processes, and exerts its biological actions through four types of histamine receptors H 1,2,3 and 4.

But it is brain mast cells, rather than microglia, which are the "first responders" to brain injury. Most importantly, activation of mast cells has been shown to activate microglia, whereas stabilisation of mast cells inhibits the CNS inflammation that would otherwise result from activation of microglial cells.

The microglial activation results in Small Fibre Neuropathy and neuropathic pain, and from this small fibre neuropathy it is believed comes the sensitisation and characteristic autonomic chaos that is POTS and POTS-like Long Covid, and this includes random symptoms such as the eye pain and anosmia in Covid.

DNA mutations in Long COVID

The DNA helps us to understand why the inflammatory response is so severe, and provides a springboard for the investigation and management of the exaggerated inflammatory and microembolic responses to the SARS-CoV-2 virus and increasingly the development of a recovery program based on individual DNA assessment matched to clinical assessment, and incorporated into current recovery programs.

Using a technique called genetic imputation, it is now possible to use the ~750,000 SNPs in an Illumina GSA sequencing machine to assess up to 83 million SNP variants with an accuracy rate of 98%.

More than 400 genes are differentially expressed in Long Covid patients. Primary problems seen from our DNA studies appear to be in the histamine pathway (affecting Mast-Cell response), along with COMT mutations affecting catecholamine (fight and flight) metabolism, as well as other mutations that alter methylation, CRP, IL-6 and responses to oxidative stress as well as the ones found at Griffith University that affect Natural Killer cell and Glymphatic function.

Other researchers, notably Prof Sonya Marshall-Gradisnik and the Griffith University Chronic Fatigue team working with TRPM3 function in the research into chronic fatigue at Griffith University have linked mutations in this pathway with “glymphatic” function and fatigue and the therapeutic benefit of *Low Dose Naltrexone*.

A single mutation, by itself, may be insufficient to cause the symptoms of Long Covid. However, we have been recognising patterns that allow clinicians to treat Long COVID. As the sensitisation from the microglial activation and small fibre neuropathy is controlled, we can work with lifestyle change, epigenetic modification, and a style of acupuncture that targets the autonomic instability, and with appropriate physiotherapy to control the mechanical drivers. Many of the simpler Long COVID require only mast cell blockade and attention to diet and lifestyle.

The mutations seen explain the underlying pathology that is occurring in the Covid-triggered POTS and it will take a larger cohort to confirm this is occurring throughout all the Long Covid subtypes. The mutations below are typical of those found in POTS and Long Covid. Long Covid is so complex and symptoms and co-morbidities so varied that detailed DNA is of enormous benefit to assess the molecular malfunctioning causing the symptoms.

There are various sub-types we are seeing that will require a larger cohort to fully assess.

Arguably the most important when looking at recovering Long Covid patients, there are mutations in mast cell function - one on the membrane and in two critical enzymes (namely DAO & HNMT) involved in clearing Histamines in different tissues in the body.

- **Mast cell mutations** that affect body’s ability to respond to mast cell activation and threats mediated through mast cells. These are major mutations in POTS and thus far in Long Covid. The primary ones are on the mast cell membranes and in the function of HMNT and Dao and enzyme. The mast cell is a potent immune cell known for its functions in host defence responses and diseases, such as asthma and allergies. Mast cells play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury. An abundance of mast cells reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts.)

- **COMT mutations** (= reduced ability to process catecholamines and oestrogen with implications in malignancy, rheumatoid arthritis and SLE) Catechol-O-Methyltransferase (COMT) is one of several enzymes that degrade catecholamines eg dopamine, adrenaline, nor-adrenaline, catecholestrogens and various drugs.
    - COMT gene production is itself influenced by methylation. Usually, methylation shuts down gene production.
    - Oestrogen also signals mast cells to release histamines via its ER receptor on Mast cells. This is a critical mutation in some.
    - There is an association between COMT mutations with malignancy especially breast cancer, and also endometriosis and auto-immune disease.
- **Oxidative stress and mitochondrial mutations-** eg eNOS, SOD2. NO metabolism-associated with the development of FMS and pain sensitization, and a likely problem in Long Covid.
- **Inflammatory mutations-** various mutations in interleukins.
- **Methylation mutations** (especially MTHFR) the 677 MTHFR mutation typically is associated with increased homocysteine, and affects collagen function via SAMe and other molecules as well as increased thrombotic risk, and plaque formation in different tissues.
- **TRP mutations**- TRPM3 appears critical in NK (Natural Killer) immune cell function, with implications for Ca2+ signalling and cell function. The transient receptor potential melastatin subfamily 3 (TRPM3) is one of the most primitive receptors in the body, activated by a wide variety of agents, from bacteria and viruses to temperature and environmental factors such as perfumes. This diversity made it a logical suspect for a condition like CIFS/ME that has so many different triggers in different people.
    - The Griffith University Chronic Fatigue team working with TRPM3 function in the research into chronic fatigue at Griffith University have linked mutations in this pathway with “glymphatic” function with consequent reduced clearance of waste solutes from the brain with production of fatigue and brain fog and the therapeutic benefit of *Low Dose Naltrexone*
    - TRPA1 is a key ion channel that detects oxidative stress and a range of endogenous and exogenous chemicals (smoke, solvents, cold air).
    - TRPM3 activity is impaired in CIFS/ME patients suggesting changes in intracellular Ca^{2+} concentration, which may impact Natural Killer (NK) cellular functions. This investigation further helps to understand the intracellular-mediated roles in NK cells and confirm the potential role of TRPM3 ion channels in the aetiology and patho-mechanism of CIFS/ME, and an equally important role in the severe fatigue of Long COVID
- **APO E4** - The Apolipoprotein E allele 4 is a major genetic risk factor for Alzheimer's disease, as this lipid carrier is important for maintaining homeostasis necessary for a healthy environment of the brain. This mutation is seen in around 15 to 20% of the general population, with 2-3% being homozygous with the increased risks that are associated. This is emerging as a significant mutation in resistant cognitive impairment.
    - APO E is particularly concentrated in astrocytic processes at the pial surface and around the blood vessels. In addition, the choroid plexus and tanycytes in the wall of the third ventricle also produce Apolipoprotein E. Thus, Apolipoprotein E production is co-localized with CSF production sites and transport pathways suggesting that lipids are transported by the glymphatic system.
    - The glymphatic system is thought to play a central role in macroscopic distribution of lipids in the brain and that medium to large lipid soluble molecules might require carrier particles in order to be delivered via the CSF. Astrocytes thus play a key role in lipid synthesis and lipid distribution by releasing lipid carrier proteins, such as Apolipoprotein E, and in maintaining the highway for distribution, the glymphatic system.

- APO E4 mutation also affects arteries, significantly increasing coronary artery disease risk ,decreased mitochondrial function, decreased insulin sensitivity, increased insulin resistance, fatty liver and progression to cirrhosis (APO E4 contributing to increased atherosclerosis).

Natural Killer Cells distinguish malignant from healthy cells, while type I and III interferons (IFNs) are innate cytokines important in the first line defence against SARS.

The TRP mutations found at Griffith affect natural killer cell function. Complicating this, COVID has evolved mechanisms to evade the antiviral function of Interferon-1 and patients show limited Interferon-1 responses, while there was an increased expression of IL-6, TNFα and other chemokines.

Possible implications of this are in an increased malignancy rate, and severity of malignancy at presentation following SARS infections. There are no published figures on post-Covid malignancy up to this point, but anticipated to become an increasing concern in the next 1 to 2 years.

The Glymphatic System

The Glymphatic System was discovered in 2013. It is basically the sewer of the brain, and dysfunction and obstruction to its flow is a major part of new work, not only in brain fog in POTS and Long Covid, but also in migraine, Parkinsons and Alzheimers Diseases.

The TRP mutations also affect glymphatic function, with a consequent reduced clearance of waste solutes from the brain causing fatigue and brain fog. *Low dose naltrexone*, a H4 blocker, provides a therapeutic benefit here, but it is not a universal panacea, and at times hard to use.

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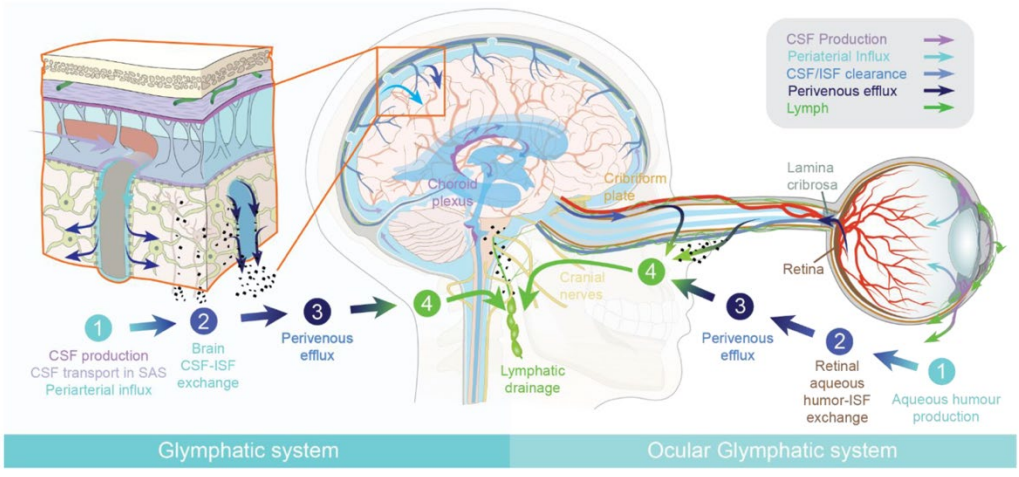

Source: Mogensen et al. The Glymphatic System (en)during Inflammation. *Int. J. Mol. Sci.* **2021**, *22*, 7491. https://doi.org/10.3390/ijms22147491

The **Apo E4** is yet another important mutation, for it a major genetic risk factor for Alzheimer's disease, as this lipid carrier is important for maintaining homeostasis necessary for a healthy environment of the brain. This mutation is seen in around 15 to 20% of the general population, with 2-

3% being homozygous with their 15% increased dementia risks. If the current research into this mutation in the cognitive impairment is confirmed, it is likely to become a major factor in assessing long term cognitive impairment. This mutation can usually be managed using available blood pressure medications Candesartan and Telmisartan. We ask that this relatively inexpensive test be made available through the PBS.

The glymphatic systems in the brain and eye export fluid and solutes from metabolically active neural tissue, and drain via the cervical lymph vessels, which empty into the venous system at the level of the subclavian veins. Glymphatic function has been shown to be affected by postural and other mechanical changes. Influences here include computer and sustained mobile phone usage.

Intriguingly, the glymphatic system functions mainly during sleep and is largely disengaged during wakefulness. The biological need for sleep may therefore reflect that the brain must enter a state of inactivity that enables elimination of potentially neurotoxic waste products, including β-amyloid.

Management:

I will restrict this section to fatigue and cognitive impairment, but we have found that other problems improve with the same basic protocols.

GPs are the logical people to deal with the complexities of Long Covid, as the problems cross many specialty areas. In rural areas, it will of course be the GPs who will carry the burden.

Modern medical management is guided in most diseases by Cochrane Guidelines which offers a conservative approach to medicine with important safeguards to patients because these discourage reckless or entrepreneurial physicians from using risky or untested practices. But such has been the speed of the diseases associated with COVID that there are no available Guidelines.

Fatigue is the most common symptom in Long Covid, often totally incapacitating.

The mitochondria are the energy sources of our cells and Covid affects the mitochondria. Dysfunctional mitochondria is associated with defective immunological response to viral infections and chronic inflammation.

There is also reactivation of other viruses especially EBV -viruses that are resident still and affect mitochondrial function.

Fatigue, though can also be from direct inflammatory or embolic damage to the heart, kidneys, liver, brain and lungs etc as well as this mitochondrial dysfunction and oxidative stress.

And it can also be impaired autonomic function from the IL-6 and TNFα driven small fibre neuropathy affecting heart function or microglial damage in the brain.

Cognitive Impairment or Brain Fog is common, just as it is in POTS and fibromyalgia, and migraine to a lesser extent.

Glymphatic flow is very important when fatigue and cognitive impairment are present. This usually improves with good posture and *low dose naltrexone (LDN)*.

Interestingly this often improves with diet change, opening the door to research into the gut-brain axis and the association with Mast Cells in the gut as symptoms usually improve with H1/H2 blockade, and frequently LDN.

Medication

Long Covid's various forms can usually be treated, often very quickly, cheaply and easily using predominantly old medication, Histamine H1 and H2 blockers, that blocks Mast Cells, and this reduces the actual COVID severity as well as managing many of the symptoms of Long COVID.

Stop the ongoing inflammatory processes. Each area of inflammation from the Covid and pre-Covid state needs to be identified and managed.

Medication starts with control of the inflammatory process to control the "microglial sensitization" from microglial inflammation.

1. **Initial medication**

    - **H1blockade:** *Fexofenadine* 180 bd (or alternative)
    - **H2 blockade:** *Famotidine* 40 or Nizatidine 300 bd if tolerated. This blocker affects Toll Receptor 3 over-expression, and from our observations does appear to provide the best results.

2. **Next stage of management**

    - **H4 blockade:** *Low Dose Naltrexone* -improves glymphatic function (and probably NK cell function). Recommend delay of 1 to 4 weeks before starting LDN as improvements with H1/H2 blockade can be assessed and are usually sufficient If H1/H2 not tolerated, caution with *Low Dose Naltrexone* (H4 blockade)
    - LDN needs to be started at a low dose. Our clinic uses 0.5 mg daily, increasing weekly to a maximum of 4.5 mg

Acute disease and protection protocol is:

- Fexofenadine 180 mg + Famotidine 40 mg, 1 each daily, twice daily if contracts COVID or in high risk situations, eg cruises, planes, buses etc. They do not appear to need to be taken every day unless going into a risk area (which may in extreme times be leaving the house).

This same protocol reduces the disease severity when contracted. No studies have been done in comparison to anti-viral treatment and currently it is utilized in our clinic in conjunction with anti-virals as per HIC guidelines.

Complementing medication:

- Support associated psychological damage

- All post-COVID needs a progressive return to physical activity and exercise as deconditioning causes deterioration- start assessment at 6 to 8 weeks post infection.

- Acupuncture assists controlling autonomic instability

The most effective methods we have found to deal with the with the **mitochondrial dysfunction** largely responsible for fatigue, cognitive impairment, low energy and memory loss has been:

- Keto /low histamine diet (low histamine major importance if has HNMT, DAO enzyme defect found on DNA or close questioning on mast cell disorders). At a minimum avoidance of all food the body reacts to as this provokes an inflammatory reaction.

Red flags here includes lack of response within 4 weeks of mast cell blockade- look for other factors, especially for inability to cope with a low histamine keto diet, and autonomic instability. All POTS-type Long COVID have mechanical drivers that require sorting.

When watching an elevated D Dimer (measuring microembolic processes in place) that will not settle, check for inflammatory problems elsewhere driving this

- Malignancy.
- Sustained stress
- Autoinflammatory disorders
- Diabetes, insulin resistance, fatty liver

The details on the protocols and background research we have employed are freely available for any doctor through PHN Gold Coast