



ORIGINAL RESEARCH PAPER

General Medicine

THE LONG COVID SYNDROME – IS IT HERE TO STAY?

KEY WORDS:

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The term Long Covid syndrome was coined by Dr. Elisa Parego. It is defined as persistent symptoms after 3 months with a past the history of SARS Cov2 infection and the symptoms not being explained by any other disease. SARS Cov2 infection originated in Wuhan, December 2019, when it jumped from bats to man, as the theory goes. As per the world data, till date, total numbers of SARS Cov2 infection were 61 crores, and the deaths were 65 lacs. In the United States of America, total numbers of SARS Cov2 infection were 9.5 crores and deaths were 10.5 lacs. In India, the numbers were 4.5 crores, and the deaths were 5.3 lacs. In our set up, the Tata Main Hospital, Jamshedpur, Jharkhand, one of the major hospitals catering to covid patients, total numbers of SARS Cov2 infection were 7840 admissions and 1162 deaths. Total numbers positive with SARS Cov-2 were 27207 in Jharkhand and deaths were 4.42 lacs.

The term '**long COVID**' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

Around 144 million people all over the globe have been affected by long covid, and it ranges from 4 to 30%. These patients might get better with treatment.

Risk factors include old age, obesity, severe disease, recurrence, females, poor pre pandemic mental health, poor general health, smoking, COPDs , severity of acute covid 19 infection and genetic predisposition.

Investigations and bio-markers for the Long Covid Syndrome [2]

In mild disease, no investigations are required. In moderate disease, C- reactive protein (CRP), d-dimer, blood sugar 48 to 72 hourly, complete blood count including neutrophil-lymphocyte ratio (NLR), kidney and liver function tests 24 to 48 hourly is required.

Pathological investigations:

Investigations in Long Covid should be ordered after confirming an initial COVID-19 infection and ruling out other diseases that may present with similar symptoms. The biomarkers reflecting the uncontrolled immune system activation are ordered.

A. General:

- i) Hematological – Lymphopenia, Neutrophilia, increased NLR, Thrombocytopenia, Depletion of CD4 & CD 8 cells, Neutrophil extracellular traps (NETs): Neutrophilic Elastase, Citrullinated histone H3, cell free DNA. Mast cell activation markers which include plasma prostaglandin D2, Histamine, heparin, Serum tryptase, Chromogranin A
- ii) Inflammatory cytokines - IL-6, IFN γ and TNF- α
- iii) SAAF- Serum Amyloid A – Persistent clotting protein [5].
- iv) Residual viral proteins within tissues – PCR, IHC & ISH- In situ Hybridization

b. Special investigations – System wise:

Central and peripheral nervous system

- Inflammatory markers – IL 18, IL 6, IL8, interferon γ (IFN- γ), IFN α 2, interleukin (IL)-1 β , IL-10, IL-17a, IL-8
- IgG oligoclonal bands -in CSF & Serum
- Anti GFAP (Glial Fibrillary Acid protein) – Antibodies against the neural Antigens
- Neuro Axonal damage – 14-3-3 protein & NFL – Neurofilament light chain protein.

Cardio-Vascular markers include troponin, BNP – Beta natriuretic peptide, creatinine Phosphokinase (CPK), Lactate Dehydrogenase (LDH), Serum Amyloid A (SAA) and alpha 2 antiplasmin.

Lung markers include Inter- leukin 6 (IL6), Transforming growth factor Beta (TGF Beta) and Fibroblastic growth factor (FGF)

Genetic susceptibility of COVID-19 is seen in patients with ACE2 polymorphism who have type 2 transmembrane serine proteases (TMPRSS2). Patients possessing HLAB15:03 genotype may become immune to the infection.

Pulmonary manifestations

Definitions

Acute COVID-19

Signs and symptoms of COVID-19 for up to 4 weeks.

Ongoing symptomatic covid

COVID-19 Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.

Post-COVID-19 syndrome

Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body.

Symptoms

Respiratory symptoms include breathlessness and cough. Cardiovascular symptoms include chest tightness, chest pain and palpitations. Generalised symptoms include fatigue, fever and myalgia.

Pathology [2]

Viral infection leads to activation of immune system and along with killing of virus also causes tissue injury through various cytokines and inflammatory mediators like GMCSF, IL-6, IL-8, IL-18, TNF alpha, The three stages of covid 19 infection are an exudative phase, proliferative phase and fibrotic phase. These changes along with microthrombi (due to endothelial injury) are responsible for both the acute as well as the long covid symptoms.

Why?

It could be direct toxicity of the virus (lungs, brain), immune dysregulation, hypercoagulability and increased RAAS activation.

Mechanism-

Persistence of viral fragments, re-infection, physical deconditioning, formation of auto antibodies, stress and persistence of spike proteins can cause the long covid syndrome.

Assessment

This should include a proper history, ruling out other comorbid diseases like anxiety, depression, GERD, BA and heart diseases. We should assess the functional status of the lung by spirometry and Diffusion Capacity of lung for Carbon dioxide (DLCO), the structural status of the lung by HRC T thorax. We should look for deconditioning of the patient in the form of weight gain, loss of muscle mass and immobility. Routine blood tests for assessing liver and kidney function, haemoglobin, electrocardiography (ECG), echo cardiography (ECHO), cardiac stress test and coagulation parameters including d-Dimer test (if more than 1000 then to be planned for a CT pulmonary angiography to rule out pulmonary embolism).

Treatment

1. Self-monitoring at home – pulse, oxygen saturation, BP, Blood sugar,
2. Treatment of comorbid conditions
3. Structured exercise program, maintain ideal body weight, healthy diet
4. Patients with evidence of post covid fibrosis on HRC T thorax and decreased functional status on spirometry and DLCO can be started on antifibrotics like Perfenidone and Nintedanib
5. Oxygen supplementation for patients who do not maintain oxygen saturation > 90%
6. BIPAP may be required for selected patients
7. Patients with severe lung damage with non-resolving respiratory failure can be put up for lung transplantation

Neurological manifestations

Long Covid Syndrome (6, 7, 8)

1. Acute manifestations of COVID-19 infection:

SARS-CoV2 is a single stranded, positive sense RNA virus. It is a neurotropic and neuro-invasive virus, the nervous system is affected not only primarily by direct infection but also secondarily through systemic complications. Infection of nervous system occurs by interaction of viral spike protein to ACE2 receptor.

Potential mechanism of Neuro-invasion

- **Neuronal retrograde spread:** via invasion of peripheral nerve terminal and then retrograde spread to the nerve synapses and then trans-synaptic transfer by either endo/exocytosis.
- **Olfactory aspiration.** Direct infection via olfactory nerve which help by its anatomy and proximity to the fore brain.
- **Viremia/Trojan Horse Mechanism.** Hematogenous spread through infected leukocytes that breaches the inflamed blood-brain barrier in the presence of an inflammatory milieu (cytokine storm).
- **Neuro-invasion via enteric pathway.** The viral fragments infects the gut and then reaches the CNS via vagal afferents.

Neurological manifestation varies from mild symptoms such as headache, anosmia, dysgeusia, myalgia and dizziness to severe manifestations like stroke, meningitis, meningoencephalitis, encephalitis and Guillain Barre Syndrome (GBS). The frequency of these occurrence varies across different studies. A Chinese retrospective study

reported neurological symptoms in 36.4% cases, whereas a French study a whopping 84%. Stroke is the most common debilitating neurological disorder with predilection for elderly and male population. 70% were ischemic strokes with traditional risk factors of ischemic stroke and cardio-embolic stroke likely due to COVID-19 associated cardiac disorder (arrhythmia, MI, Myocarditis, Heart failure) leading to cardio-embolic stroke and cerebral vein thrombosis due to a prothrombotic state induced by COVID-19 infection.

The GB Syndrome can occur as a para-infectious and post infectious complication with onset after 5-10 days of exposure, but an epidemiological study in the UK failed to prove the association between COVID-19 and GBS.

Other reported complications in acute COVID-19 are ADEM (Acute Disseminated encephalomyelitis), Acute hemorrhagic leukoencephalitis (AHL), Transverse Myelitis, PRES (Posterior Reversible Encephalopathy Syndrome), Opsoclonus-Myoclonus Syndrome, Focal and Multifocal Neuropathies, critical illness neuropathy and myopathy and peripheral nerve injuries after prone position ventilation (Brachial Plexus).

2. Long Covid syndrome pathophysiology [2]

Long Covid (LC) has a broad range of symptoms (physical and mental) and symptom clusters that develop during or after COVID-19, continue for ≥ 2 months (i.e., 3 months from onset of illness) have an impact on the patient life and are not explained by an alternative diagnosis.

Several overlapping pathological mechanisms of neurological manifestation of acute COVID-19 have been established, including viral neuro-invasion accompanied by aberrant neuro-immunological response, endotheliopathy associated with blood-brain barrier dysfunction, coagulopathy, that precipitate hypoxic-ischemic neuronal injury, metabolic imbalance, oxidative stress cascade and cellular apoptosis, but in the absence of diagnostic markers and robust neuropathological data, most published article have so far proposed putative pathophysiological mechanisms for neurological 'long-COVID'

The most frequent neurological manifestation of LC encompass fatigue, brain fog, headache, cognitive impairment, sleep, mood, smell and taste disorder, myalgia, sensorimotor deficit and dysautonomia.

3. Management of long COVID-19

Time to symptom resolution appears to depend on previous comorbid risk factors, severity of acute illness and spectrum of symptoms experienced by the patient.

A longer recovery is expected in patients requiring hospitalization, older patients with preexisting comorbidities, patients who experience medical complications, and prolonged stay in hospital or ICU. However, data also suggest that those with less severe disease not hospitalized or self-reported COVID-19 have often reported prolonged and persistent symptoms [3, 4]. To date, there is very limited evidence that pharmacological approaches could be effective in the treatment of neurological long COVID sequelae.

Altered taste and smell: the majority have completed or near completed recovery at one to three months, although a small proportion (<5%) of symptoms persisted longer. Patients with persistent gustatory and/or olfactory dysfunction may benefit from olfactory training and self-guided programs available online.

Fatigue, poor endurance, and functional status: General guidance for management of patient with persistent fatigue includes:

- Adequate rest, good sleep hygiene, and specific fatigue management strategies- 'four-P' approach to energy conservation: Planning, Pacing, Prioritizing, and Positioning.
- Graded exercise therapy- to improve endurance and reduce fatigue.
- There is currently no evidence for the use of specific pharmacologic agents in the treatment of fatigue.
- In recent RCTs, supplementation with systemic enzyme complex (Immuno SEB) and probiotics complex (Probio SEB CSC3) resulted in greater attenuation of physical and mental fatigue scores in treated patient than placebo. However despite several methodological limitations, these findings warrant replication in future, large well designed RCTs.

1. Myalgic Encephalomyelitis (ME)/ Chronic Fatigue Syndrome (CFS) and Brain fog

A wide variety of infectious agents have been reported to be associated with a postinfectious fatigue illness resembling ME/CFS, includes Epstein-Barr virus, Ross River virus, Coxiella burnetti (Q fever), Ebola virus, and SARS-CoV-2..

ME/CFS is a chronic complex illness with multisystem manifestations and long-term impact on functional impairment.

The hallmark of ME/CFS is persistent and unexplained fatigue resulting in significant impairment in daily functioning along with worsening of symptoms following physical or mental exertion that would have been tolerated before illness (post-exertional malaise), that is unremitting even with rest.

ME/CFS is 3-4 times more common in female, in 40-50 years age group.

Diagnostic criteria given by IOM-2015.

Brain fog term used to describe the feeling of being mentally sluggish and fuzzy. It can be symptoms of other health conditions.

it feels like a lack of mental clarity; difficulty in focusing, thinking and recalling things.

Caused of brain fog in general are.

- Lack of sleep
- Depression
- Dementia
- Perimenopause
- Medication
- Hypothyroidism
- Vitamin B12 deficiency
- Chronic health condition like multiple sclerosis
- Post Covid-19

Tips and trick to improve Brain fog.

- Get enough sleep: fixed sleep schedule, 7-9 hrs of sleep, sleep hygiene
- Try new things: engaged the mind in mentally stimulating activities.
- Avoid multitasking: focusing one thing at a time.
- Work on your memory: rhymes, mnemonics, or visual or verbal cues.
- Take mental break: close your eyes, take a short walk, or look out your window.
- Focus your attention.
- Engage in deep thought:
- Try meditation.
- Exercise regularly.
- Follow a healthy diet: Mediterranean diet, olive, fruits, nuts, beans, and vegetable.
- Avoid alcohol and drugs

Neuropsychiatric manifestations of Long covid syndrome

During the acute phase of covid -19, apart from the typical systemic and pulmonary manifestations many patients manifest neuropsychiatric symptoms like hyposmia, anosmia, altered consciousness, delirium, agitation, vertigo, numbness, paraesthesia, insomnia, anxiety and depressive symptoms and rarely new onset acute psychosis. As per the landmark study published in Lancet where they have evaluated 236379 patients diagnosed with covid 19, the estimated incidence of neuropsychiatric disorders following 6 months of infection was 33% with 13% receiving their first such diagnosis. For patients admitted in intensive care unit the incidence was 46.4% with first diagnosis being 25%. Various neuropsychiatric disorders reported in long covid syndrome are depression, anxiety disorder, post-traumatic stress disorder, sleep disorder, cognitive disorder, chronic fatigue, dementia, and psychosis. Among this anxiety disorder, depression and cognitive disorder are commonly seen. Various etiological factors have been proposed for the possible reasons for neuropsychiatric manifestations. The direct causes are attributed to neuroinvasive and neurotropic property of covid 19 virus, rapid overproduction of cytokines and immune cell hyperactivation. Indirect contributing factors are social isolation, loneliness, uncertainty of prognosis, incomplete recovery in physical health, changes in sleep and lifestyle behaviour and economic burden. Other risk factors include female sex, presence of physical comorbidities, history of psychiatric illness. There is no specific guideline for the treatment of neuropsychiatric disorder in long covid. Individual cases are managed as per the symptomatology. Psychotherapy and lifestyle modifications play an important role in the recovery of these symptoms. SAA-4, IL-8, neurofibrillary acid protein, glial protein, growth differentiation factor are the markers to be looked for in Cerebrospinal Fluid (CSF).

CONCLUSION

As predicted by Dr. Anthony Fauci- the most renowned and revered epidemiologist from the US, the SARS Cov2 infection is going to haunt us until end 2025, so we expect that the long covid syndrome is also going to be with us till 2025. Long covid may be diagnosed late or not at all, so both generalists and specialists should be alert to it as a differential, while also being aware that patients can develop other persistent symptoms following acute covid-19 that are not necessarily caused by the virus . Community based interdisciplinary services and adequate support and training for healthcare professionals are needed to rapidly improve care and services for the growing numbers of people living with long covid.

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