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Letter to the Editor

Post-COVID syndrome: an emerging global health issue in the aftermath of the SARS-COV-2 pandemic

Sir,

SARS-CoV-19 started as acute respiratory tract infection in late 2019 and spread globally.[1] It led to 65 million people affected worldwide and deaths of multimillion across the world. The term "post-COVID conditions" is an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.[2]

FIRST INSTANCES OF THE POST-COVID SYNDROME

By late 2020 it did become apparent some people who contracted SARS-Cov-19 continued to have prolonged symptoms which were not attributable to any other illness like post COVID fatigue. There was range of symptoms from tiredness, fatigue exhaustion to extreme mast cell activation syndrome. So, far there have been more than 200 symptoms attributed to post COVID illness.

BACKGROUND AND DEFINITION

Various terms associated with this syndrome such as long COVID, Post-Acute sequelae of SARS-CoV-2.[3]

Post-COVID-19 syndrome

signs and symptoms that develop during or after COVID-19 and continue for more than 12 weeks and are not explained by an alternative diagnosis. It is a multisystem disease with over 200 Symptoms.[4]

Ongoing COVID

Symptoms persisting longer than 4 weeks till 12 weeks attributed to no other illness.[5]

For most people it is mild, and people can continue to function. For some its severe and debilitating and severely affects quality of life.

DEMOGRAPHICS INFLUENCING POST-COVID SYNDROME

Age 18-80 but predominantly middle age 40's. Gender 3:1 females to male.[6] Seems to affect people with pre-existing health conditions obesity, diabetes, autoimmune conditions, minority ethnic backgrounds.[7]

SYMPTOMS AND CLINICAL MANIFESTATIONS

Respiratory

SARS-COVID affects various systems. Its predominantly a respiratory virus and majority people develop breathing related symptoms commonest being persistent cough, dyspnoea and decreased exercise tolerance.[8] Patient describes it as constant hunger for having to take more oxygen in

This is thought to be due to reduced diffusion capacity, restrictive pulmonary physiology. These changes would be evident on imaging such as chest X-ray and high-resolution CT some of the findings will be ground-glass opacities and fibrotic changes on imaging.[9]

Figure 1: X-ray and CT appearance of acute COVID pneumonia.

Haematological/ vascular

Thromboembolic events have been noted to be <5% in post-acute COVID-19 in retrospective studies. These events are dependent on the duration of the hyper inflammatory state induced by infection. This can lead to microthrombi and microembolli and small vessel inflammation.

Direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thrombo prophylaxis after risk-benefit discussion in patients with predisposing risk factors for immobility, persistently

elevated d-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer.

Cardiology

Persistent symptoms may include palpitations, dyspnoea and chest pain. This is again thought to be due to cellular hypoxia.

Long-term sequelae may include increased cardio metabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI) manifesting with arrhythmias, tachycardia and autonomic dysfunction.[10]

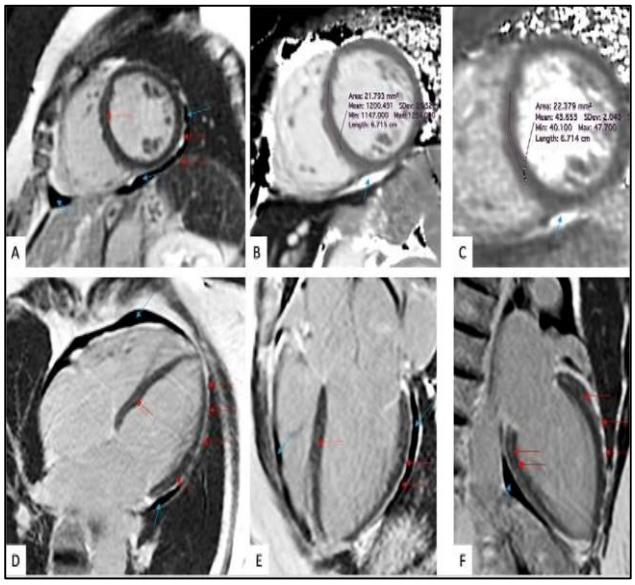

Figure 2 (A-F): Cardiac MR showing fibrosis/ scarring.

Postural orthostatic tachycardia syndrome (POTS) and inappropriate sinus tachycardia Syndrome is another rare but very distressing manifestation of cardiac sequel. Rarely it can lead to myocarditis as well.[11]

Neuropsychiatric

Persistent abnormalities may include fatigue, myalgia, headache, dysautonomia and cognitive impairment (brain fog), bladder dysfunction, taste and smell dysfunction, sleep disturbances, vivid dreams, people commonly state they are not as sharp as they use to be.[12]

Anxiety, depression, sleep disturbances and PTSD have been reported in 30-40% of COVID-19 survivors, like survivors of other pathogenic coronaviruses.

The pathophysiology of neuropsychiatric complications is mechanistically diverse and entails immune dysregulation, inflammation, microvascular thrombosis, iatrogenic effects of medications and psychosocial impacts of infection.

Renal

Resolution of AKI during acute COVID-19 occurs in most patients; however, reduced eGFR has been reported at 6 months follow-up.[13]

COVID associated acute vascular necrosis (COVAN) may be the predominant pattern of renal injury in individuals of African descent.

Endocrine

Endocrine sequelae may include new or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization.

Few cases of pancreatitis/ splenic dysfunction have also been reported.[14]

Gastrointestinal/ hepatobiliary

Prolonged viral faecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing. COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic organisms and depletion of beneficial commensals.[15]

Range of symptoms could include persistent nausea, flatulence, diarrhoea similar to visceral hypersensitivity. This is thought to be due to post viral auto dysregulation and mimics irritable bowel syndrome.

Rheumatological

Joint pains, muscle aches and pains and muscle weakness, few cases of seropositive Rheumatoid arthritis have been reported as well.

Skin

Hair loss is the predominant symptom and has been reported in approximately 20% of COVID-19 survivors. Various rashes particularly in young.

MISc (Multi inflammation syndrome in children)

It's a rare set of symptoms affecting some children diagnostic criteria: <21 years old with fever, elevated inflammatory markers, multiple organ dysfunction, current or recent SARS-CoV-2 infection and exclusion of other plausible diagnosis. [17]

It typically affects children >7 years and disproportionately of African, Afro-Caribbean or Hispanic origin. [18]

Cardiovascular (coronary artery aneurysm) and neurologic (headache, encephalopathy, stroke and seizure) complications can occur.

PSYCHOLOGICAL IMPACT

Mental health issues

including grief reactions, substance use disorders, anxiety, sleep disorders, depression, suicides, post-traumatic stress disorders, panic disorders. [19]

New-onset mental health issues

Due to COVID-19-related stress, fear and loneliness; enduring neuropsychiatric symptoms or disorders (e.g., acute ischaemic stroke, headache, dizziness, ataxia, delirium and seizures) of COVID-19 infection due to cytokine storms.

Relapse of pre-existing mental illness

Due to reduced access to therapeutic resources, disruption of therapies, service provision and social support.[20]

Suicides

Due to neuropsychiatric manifestations and the socioeconomic impact of COVID-19.[21]

Other issues

COVID-19-related stigma, discrimination and hate crimes.

Vulnerable population

Children and adolescents; elderly; unemployed and homeless persons; COVID-19 survivors; healthcare workers (HCWs); those with pre-existing psychiatric disorders; grass-roots workers; pregnant women; people with disabilities and chronic diseases; migrants; refugees; lesbian, gay, bisexual, transgender and queer (LGBTQ) community; racial and ethnic minorities.[22]

Risk factors

The death of either parent, caregivers or loved ones, misinformation, loss of peer support because of closure of school or workplace, academic loss, medical comorbidities, uncertainties, stigma, prolonged isolation, social rejection, work stress, burn-out, being in direct contact with active cases and facing economic burdens.

Frustration is very common; patient find it difficult to do day to day tasks. Other symptoms could include Anxiety, Depression, PTSD like symptoms particularly in patients admitted to ITU. [23]

Duration of symptoms varies from person to person most people get better within 12-18 months. It's a very new condition and long-term prognosis is difficult to the predict.[24]

PATHOPHYSIOLOGY AND POSSIBLE MECHANISMS

It is also possible that some patients with post-COVID conditions will not have had positive test results for SARS-CoV-2 because of a lack of testing or inaccurate testing during the acute period, or because of waning antibody levels or false-negative antibody testing during follow up.

Post-COVID conditions are heterogeneous and may be attributable to different underlying pathophysiologic processes. Researchers are working to characterize and differentiate the multiple possible aetiologies, such as damage to ACE receptors affecting transport of oxygen leading to cellular hypoxia and reduced ATP energy production.[24]

Other possible reasons organ damage resulting from acute phase infection, complications from a dysregulated inflammatory state, ongoing viral activity associated with an intra-host viral reservoir, autoimmunity, inadequate antibody response and hyperactivation of cytokine system.[25]

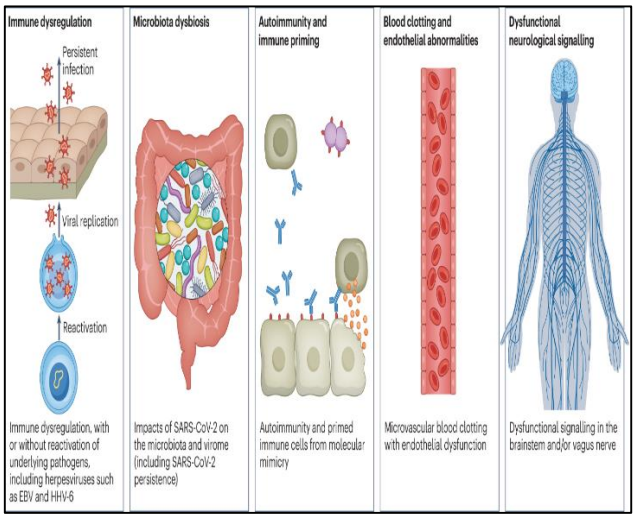

Figure 3: Hypothesized mechanism of post COVID syndrome.

In some circumstances immune system goes in overdrive during acute COVID infection as well as during post-COVID syndrome

There has been studies suggestive of raised levels of cytokines, B cells, T cells and mast cells. There is a rare condition mast cell activation syndrome which is thought to be triggered by SARS-COVID virus leading to widespread raised levels of histamine like chemicals and causing multisystem inflammation.[26]

Like other conditions such as chronic fatigue syndrome and myeloencaphalitis, post COVID syndrome is variable. Patients have good and bad days.

MANAGEMENT AND TREATMENT

Post COVID syndrome is complex condition, and it needs multidisciplinary approach.[27]

COVID clinician, rehab team (physical therapy, pulmonary rehab, cardiac rehab), occupational therapist and psychological therapy team work together to do holistic assessment on patient and come up with comprehensive individualized care plan. We have devised a system wise approach.

Respiratory

Response is based on British thoracic society guideline on the severity of acute COVID-19 and whether the patient received ICU-level care76.[28]

Algorithms for both severe and mild-to-moderate COVID-19 groups recommend clinical assessment and chest X-ray in all patients at 12 weeks, along with consideration of pulmonary function tests (PFTs), six minute walking test (6MWTs), sputum sampling and echocardiogram according to clinical judgment.

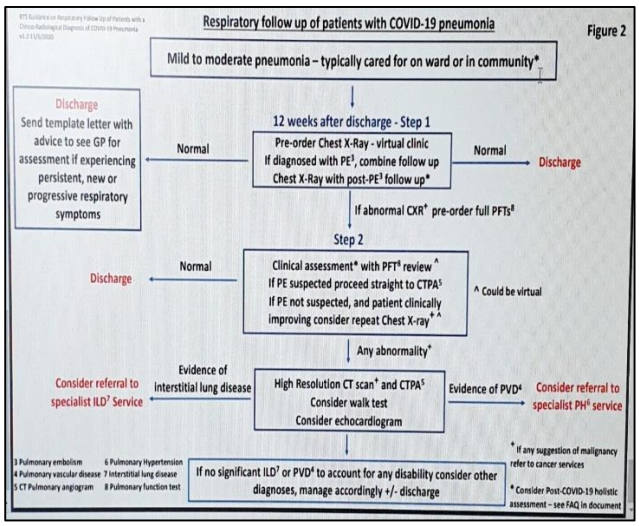

Figure 4: British thoracic society flowchart to follow up post COVID patients.

Rehab/ energy management/ gradual building up of stamina is mainstay of treatment.

Cardiovascular

Beta blockers have been used with limited success for postural orthostatic tachycardia syndrome (POTS). Patients who have asthma or where B blockers cannot be used can be tried on Ivabradine.

Patients with cardiovascular complications during acute infection or those experiencing persistent cardiac symptoms may be monitored with serial clinical, echocardiogram and electrocardiogram follow-up.[29]

Neuropsychiatric

Its complex set of symptoms and usually management will include psychological support as well as symptomatic treatment with one of the neuropathic pain killers such as amitriptyline/ gabapentin/ pregabalin.[30]

Where there is more psychological impact SSRRI's, SNRI's can be trialled.

Regular post COVID psychological therapies have shown to improve symptoms.

Endocrine

Patients with newly diagnosed diabetes in the absence of traditional risk factors for type 2 diabetes, suspected hypothalamic-pituitary-adrenal axis suppression or hyperthyroidism should undergo the appropriate laboratory testing and should be referred to endocrinology.[31]

Gastrointestinal

Patients presenting with persistent vague abdominal symptoms should be investigated to rule out inflammatory bowel disease. Once ruled out treatment would be symptomatic with antispasmodics such as mebeverine, hyoscine and spasmonal. Probiotics have shown to improve gut flora.[32]

Top tips

In our personal experience for working over last two years in post COVID clinic we have identified and created a list of modalities we have tried and anecdotally patients have found it useful. Some of those modalities we have listed here.

Psychological support/ reassurance is paramount importance. Good explanation of condition and natural course will help alleviate anxiety. Most patients in our experience will recover in 6-18 months back to their baseline.[33-35]

Breathing exercises pulmonary rehabilitation certainly improve effort of breathing and strengthens accessory muscle of breathing. Antihistamines, low histamine diet and montelukast has helped some patients

Hyperbaric O_2 has been used in research studies with variable benefits.

Zinc/ selenium supplements have helped to improve hair loss.

Rehab/ energy management/ gradual /gradient exercise programme is very useful for most patients feeling chronic fatigue and tiredness.[36,37]

For sleep disturbances sleep hygiene, regular exercise and in some cases, melatonin has been helpful.

LIMITATIONS AND CHALLENGES IN HEALTHCARE SYSTEMS

Post-COVID syndrome is very new condition with not much understanding both among physicians and patients.[38]

There is some research into this condition still it's not very well understood condition and there are not many modalities of treatment.[39]

More research is needed to understand this condition better.

Vaccination seems to help people who are not vaccinated.[40] They tend to get milder symptoms and recover quickly even if they were not vaccinated before contractive SARS-COVID. [41]

LONG-TERM GLOBAL HEALTH IMPLICATIONS

More than144 million people globally are living with multi-dimensional and episodic symptoms that broadly impact functional status and quality of life. This is compounded by economic and societal drivers contributing to an increasing burden of long COVID in the global population. Data from Chen et al highlight that the global probability of developing long COVID is 0.43 (95% confidence interval (CI=0.39-0.46) with those hospitalised being more likely to develop lasting symptoms (0.54, 95% CI=0.44-0.63) compared to those not hospitalised (0.34, 95% CI=0.25-0.46). Symptom prevalence reported at 30 days post-infection is 0.37 (95% CI=0.26-0.49), 0.25 at 60 days (95% CI=0.15-0.38), 0.32 at 90 days (95% CI=0.14-0.57) and 0.49 at 120 days 49 (95% CI=0.40-0.59).[42] Additional data highlights that the time to recovery exceeded 35 weeks in 3423 (91%) patients, reporting an average of 56±26 symptoms across different organ systems.

The episodic nature of symptoms and functioning with long COVID is reported to affect 86% of participants (95% CI=84.8%-87.0%) with symptoms triggered by exercise training, or physical or mental activity.

RESEARCH GAPS AND FUTURE DIRECTIONS

The national institute of health research and UK research and Innovation demonstrated an agile response to the COVID-19 pandemic by allocating research funding to address the immediate burden of COVID-19. While this was important for an immediate response, the long-term and unanswered challenges of long COVID should be addressed with a sustained allocation of research funding.[43]

Currently, the national institute of health is the only health research authority to make a public sustainable commitment to provide $US 1.15 billion in funding over four years for research into the long-term health consequences of SARS-CoV-2. Sustained research support is essential to addressing the needs of millions living with and those yet to develop long COVID.[44]

At present, a lack of mechanistic and clinical understanding has hampered the global response to long COVID and is in part contributing to the rise in confirmed long COVID diagnosis. In the absence of an appropriate understanding, it is difficult to design and develop support mechanisms that address the needs of patients and restorespre-COVID-19 quality of life.

CONCLUSION

Post COVID syndrome is global pandemic. Millions of people are living with symptoms which have huge impact on physical, psychological social and occupational health. It is a multisystem disease and can affect literally any part of body. It's not very well understood condition there are still lots of uncertainties and needs lots of research to understand and manage it better. Dedicated clinics, Multidisciplinary team approach will certainly help to improve understanding and management for patients suffering with impact of this new condition.

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