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From COVID-19 to long COVID; the forms of the neurological manifestations

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ABSTRACT

Ever since the SARS-CoV-2 infection was declared a global pandemic in 2020, numerous multisystemic manifestations have been discovered. The COVID-19 is known to cause a wide spectrum of neurological symptoms like fatigue, headache, brain fog, stroke, smell and taste disorders, encephalopathy and neurodegenerative disorders. The neurological manifestations are more prevalent in the post-COVID syndrome or long COVID. The National Institute for Health and Care Excellence and WHO defined Ongoing Symptomatic COVID as 4-12 weeks post infection and post COVID-19 syndrome as persistence of symptoms beyond 12 weeks. So far there are limited data available regarding the pathophysiology of neurological symptoms of prolonged COVID, although neuroinflammation and oxidative damage have been implicated. In this review article, we have highlighted the transition from COVID to long-term COVID, focusing the discussion particularly on neurological complications.

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Introduction

Coronavirus disease (COVID-19) was first described in Wuhan district of China in December 2019. WHO declared on March 11, 2020, the novel coronavirus (COVID-19) outbreak a global pandemic which led to the havoc the world went through with multiple waves and variants, currently 587,396,589 confirmed cases and 6,428,661 deaths have been reported [1].

Variants of concerns since the start of pandemic included Alpha, Beta, Gamma and Delta (SARS-CoV-2 lineages/ Pango Lineages of concern: B.1.351, P.1, and B.1.617.2 respectively). Currently the predominant "Variant of concern" circulating world over is Omicron (SARS-CoV-2 lineage/ Pango Lineage: B.1.1.529) [2].

The initial manifestation noted was a respiratory tract infection, however it soon it became clear that it is a multisystem disease, which could be attributed to the tendency of virus to gain entry into endothelial cells via Angiotensin converting enzyme 2 (ACE2) receptors. The virus is known to inhibit ACE2, which is responsible for breakdown of Angiotensin II, a pro-inflammatory marker [3]. The indirect effects of the virus are mediated through cytokine storm leading to increased levels of TNF-α, IL-1 and chemokines, increasing the risk of multiorgan dysfunction [4].

As the humanity seemed to be having a sense of relief from COVID-19, due to decreasing number of cases and severity post-vaccination and post-infection immunity, several survivors' studies have highlighted the havoc COVID-19 survivor are suffering from, including mortality post-COVID-19 [5].

Discussions

Long COVID

Long COVID or post-acute sequelae of SARS-CoV-2 (PASC) is defined as persistence of relapsing remitting or continuous symptoms weeks to months after the expected period of clinical recovery. It is usually associated with multiple biochemical, radiological and microbiological recovery manifestations [6].

Based on the duration, it can be classified as:

- Post-Acute COVID where symptoms last between 3-12 weeks.
- Chronic COVID where symptoms last beyond 12 weeks.

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Risk factors associated with development of post COVID syndrome include women, increased age, other co-morbidities and presence of more than 5 symptoms at first presentation [7].

The WHO defines Post COVID-19 condition as the disease seen in people with a history of probable or confirmed SARS-CoV-2 infection; within three months from the onset of COVID-19, and with effects that last for at least two months [8].

The commonly associated symptoms of PASC include-fatigue, dyspnea, joint pain, chest pain, cough, headache, diarrhea, cognitive blunting (brain fog) along with mental issues like depression, anxiety, sleep disorders and post-traumatic stress disorder. The prevalence of the long-lasting residual symptoms was higher (87%) among hospitalized patients as compared to patients treated on an outpatient basis. It was observed that more than 50% of patients showed fatigue at around 10 weeks following the SARS-CoV-2 infection [9].

Two patterns of symptoms have been described in PASC [6,7]:

- Fatigue, headache, persistent cough, shortness of breath, sore throat, loss of smell and taste.
- Multiorgan involvement (myocardial infarction, cardiac failure, myocarditis, stroke, altered mental status, post-traumatic stress disorder, neuro-degenerative disorders) with fever and gastrointestinal manifestations (abdominal pain, nausea, irritable bowel syndrome, altered bowel motility).

Pathophysiology of Neuropsychiatric Manifestations in COVID-19

The proposed mechanisms for the above manifestations include viral infiltration into the brain, autoimmune response following viral infection, cytokine dysregulation and peripheral immune transmigration [10-12]. The pathophysiology is summarized in Figure 1.

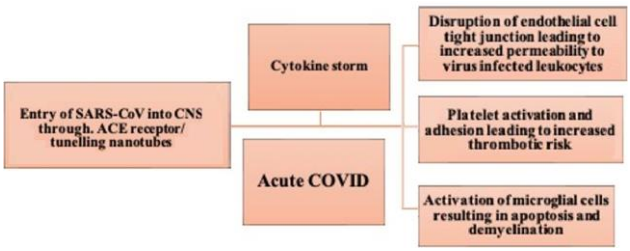

Figure 1. Pathogenesis of Acute COVID

Neurological Manifestations of COVID-19

Apart from the respiratory symptoms of COVID-19, it has been associated with neurological manifestations ranging from central nervous system to peripheral nervous system and neuromuscular symptoms.

Nalleballe et al. in their study on neuropsychiatric manifestations of COVID-19 described headache as the most common presentation (3.7%) followed by sleep disorders (3.4%), encephalopathy (2.3%), myalgia (2%), agnosia/ ageusia (1.2%), stroke (1%), seizure (0.6%) and dizziness (0.5%) (Figure 2) [13].

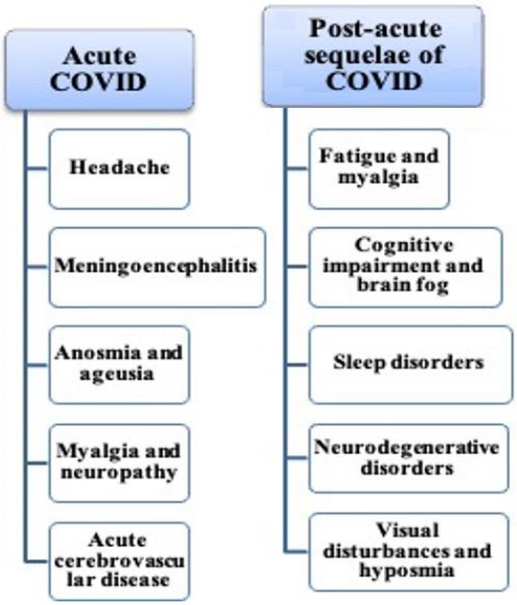

Figure 2. Important neurological manifestations of Acute COVID and Post-Acute sequelae of SARS-CoV-2

Headache

Headache is the most common neurological finding in patients of COVID-19 with a prevalence of 6.5-34% [14].

In a study conducted in Brazil, headache was found to be the second most prevalent neurological symptom after focal neurological deficit. They concluded that patients with headache were more likely to have fever. The headache was found to be frontal or holocranial [15].

The possible mechanism suggested may be direct invasion of the trigeminal endings or a cytokine storm resulting in release of NF-κB, Prostaglandin E2, IL-1β, nitric oxide, TNF-α and reactive oxygen species activating the trigeminal nerve endings [16]. The vascular theory leading to endothelial dysfunction and inflammation may also result in trigeminal activation and headache [17].

In another study conducted in Turkey, headache was found to be the most common symptom, which was more prevalent in men which may be attributed to the protective role of female hormones or the presence of ACE2 on X chromosome [18].

Encephalopathy and meningoencephalitis

Encephalopathy, which is defined as diffuse brain dysfunction, manifests as altered mental state ranging from confusion, delirium to coma. Encephalitis, defined as acute diffuse inflammation of the brain, manifests as fever, seizures, headache, focal neurological deficit and altered consciousness. Meningitis is characterized by fever, headache, vomiting and meningeal signs [19].

Encephalopathy is the most common severe manifestation of COVID-19, reported in up to 55% of critically ill patients [20]. Beach et al. described two hypotheses for the pathogenesis of encephalopathy in SARS-CoV-2 infection. The virus may invade the brain directly via synapse pathway extending from pulmonary chemoreceptors to the medullary cardiorespiratory center. The second hypothesis described is the secondary systemic mechanism, which has 2 pathways- immune response mediated and acute respiratory distress syndrome (ARDS) mediated. In hypoxemia, hypoperfusion, oxidative stress from ARDS and uremia could result in encephalopathy. The immune response mechanism results in cytokine storm with breakdown of the blood brain barrier [21].

Meningoencephalitis is an infrequent neurological manifestation seen in only 0.5% of cases in the GCS-Neuro COVID study [22].

CSF examination in COVID-19 induced encephalitis may show lymphocytic pleocytosis and increased protein. Viral RNA has also been isolated from CSF in majority cases of encephalitis [23]. An indirect enzyme linked immunosorbent assay in CSF to detect IgM for SARS-CoV-2 has also been used to confirm the diagnosis of viral encephalitis [24].

SARS-CoV-2 can also cause postinfectious encephalomyelitis, an autoimmune demyelinating disease of brain due to molecular mimicry of virus with myelin autoantigens [25].

Anosmia and ageusia

The onset of olfactory dysfunction appeared simultaneously or immediately after the onset of other COVID-19 symptoms. However, in about 63% cases, it persisted after resolution of the other symptoms [26].

The anosmia may be attributed to viral damage to the olfactory bulb or indirect damage to the neuronal cells by targeting sustentacular cells, Bowman's gland cells and vascular pericytes of olfactory epithelium [27]. The persistent dysfunction may be caused by stem cell injury.

ACE2 is responsible for modulating taste perception. ACE2 receptors are expressed diffusely on mucous membrane of the tongue and the SARS-CoV-2 attacks through the ACE2 receptor, which may be responsible for the ageusia [28].

Alternatively, the virus could bind sialic acid on taste buds promoting breakdown of the gustatory particles. Sialic acid, which is a component of salivary mucin, protects glycoprotein transporting gustatory particles from enzymatic degradation [29].

Myalgia and neuropathy

Muscle pain specially in the proximal muscles along with muscle weakness are frequent neurological manifestations of acute COVID. However, it is not uncommon for these symptoms to persist up to 6 months after acute infection. The workup of these symptoms includes clinical history, neurological examination followed by laboratory investigations like myoglobin, creatine kinase, erythrocyte sedimentation rate along with CSF examination [30].

Acute cerebrovascular disease

The reported incidence of acute cerebrovascular disease in COVID-19 patients ranged from 0.4-8.1% [31].

Among these, acute ischemic stroke and intracerebral hemorrhage constitute 87.4% and 11.6% respectively. The most common mechanism in ischemic stroke was cryptogenic followed by cardio-embolism and large vessel atherosclerosis.

In comparison to strokes without COVID-19, patients with cerebrovascular disease and COVID were younger, had a severe presentation, which was often caused by large artery occlusion [32].

Severe COVID-19 is associated with 'sepsis induced coagulopathy' leading to increased fibrinogen and D dimer and antiphospholipid antibodies along with cytokine storm which contributes to increased thrombosis. Direct viral invasion of the endothelial cells leads to endothelitis further adding to the cascade. Inhibition of ACE2 receptor results in unopposed Angiotensin II, which causes endothelial dysfunction, increased sympathetic activity, vasoconstriction and organ ischemia [33].

The factors implicated in pathogenesis of intracerebral hemorrhage include direct viral damage to the intracranial arteries leading to wall rupture. The virus induced downregulation of Renin-Angiotensin system results in raised blood pressure, which along with cytokine induced breakdown of blood brain barrier, result in increased risk of hemorrhagic stroke [34]. Metabolic acidosis or disseminated intravascular coagulation may induce a consumption coagulopathy resulting in increased risk of hemorrhage [35].

Pathogenesis of PASC

The virus induced neuro-inflammation along with hypoxic, pro-thrombotic and metabolic cascades is responsible for the pathogenesis of neurological symptoms of PASC [36,37]. The role of neuroinflammation has been illustrated by numerous studies which have shown abnormal humoral and cellular responses, elevated levels of IL-6 and autoantibodies directed against cellular receptors in PASC which may be responsible for the long-term sequelae [38-41]. The augmented expression of PECAM-1 along with raised tissue factor and von Willebrand factor levels, all suggest activation of the coagulation system leading to a prothrombotic state and occlusion of the small vessels [42].

A reduced effector molecule observed in memory T cells showed a significant association with severity of cognitive impairment [43].

The blood barrier dysfunction along with hypercoagulable state is implicated in precipitation of cerebrovascular disease and hypoxic- ischemic injury [44].

The involvement of the gastrointestinal tract and the brain gut axis has also been implicated in the neurological symptoms of PASC as prolonged shedding of the virus has been observed in the gastrointestinal tract up to 3 months post-acute infection [45].

A study was conducted to evaluate the biomarkers of neuronal and astrocytic injury (Neurofilament light chain, Glial fibrillary acidic protein, Growth differentiation factor 15). They demonstrated raised levels of the biomarkers in the acute phase of infection, which normalized at 6 months follow-up. However, the neurological symptoms, which were persistent at 6 months follow up included fatigue (40%), brain fog (29%) and cognitive changes (25%) [46].

Another study observed that the prevalence of neurocognitive symptoms was higher in patients with greater anti-nuclear antibody titer (≥1:160) which hints at the role of autoimmunity in neurological complications of PASC. Mannose binding lectin and IL-8 have also described as probable biomarkers but they are yet to be used widely (Figure 3) [47]. Elevated plasma levels of IL-6, monocyte chemoattractant protein 1 and tumour necrosis factor α have been observed in patients exhibiting symptoms of post-acute sequelae of COVID-19 [48].

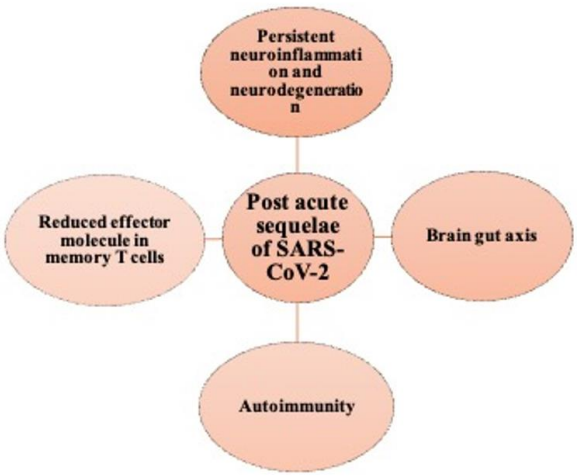

Figure 3. Pathogenesis of Post-acute sequelae of COVID

Neurological Sequelae of PASC

The long-term neurological complications of PASC are highly prevalent with almost 1/3rd patients presenting with symptoms in the six months following infection.

Old age, other comorbidities and severity of the infection were found to be the predictors of neurological manifestations associated with PASC. Pilotto et al. observed that around 40% of COVID-19 patients at 6 month follow up demonstrated objectifiable abnormalities on neurological evaluation with most prevalent being hyposmia and cognitive deficits [49].

The most common neurological symptoms associated with PASC include fatigue (34%), memory decline (31%), sleep disorders (30.8%) and myalgia (29.6%) followed by visual disturbances and hyposmia. The incidence of cognitive symptoms like memory decline was higher in moderate to severe COVID as compared to other symptoms like myalgia which were independent of severity. This may be attributed to increased vulnerability of central nervous system to severe COVID infection due to greater inflammatory response and longer hospitalization [49]. Myalgia and hyposmia develop during acute COVID, however persistence of these symptoms may be observed post-infection. The persistent symptoms may arise following the long-term presence of SARS-CoV-2 RNA in brain tissue leading to neuronal loss. Further, the blood brain barrier dysfunction may result in entry of inflammatory cells thus promoting persistent neuro-inflammation [50].

Fatigue and myalgia

Fatigue, which is the most frequent manifestation of PASC may result from the unresolved inflammation after acute infection resulting from viral persistence, lymphopenia and gut dysbiosis. Li et al. demonstrated significant viral RNA shedding even 3 months after infection while SARS-CoV-2 proteins and nucleic acids have been isolated in around 50% of asymptomatic patients four months after acute infection. Prolonged fecal shedding of SARS-CoV-2 and elevated levels of inflammatory markers also results in unresolved inflammation [51]. Autonomic system dysfunction, inadequate cerebral perfusion, reduced neurotransmitter levels and decreased neuronal excitability are other factors which may also be responsible for the fatigue and myalgia [52].

Cognitive impairment

Hartung et al. in their study, reported 26% and 1% of patients with mild and moderate cognitive impairment 9 months after acute infection. Cognitive impairment was best determined by pre-COVID neurological comorbidity and socio-demographic factors. They found about 5% of patients with both cognitive impairment and fatigue, though there was no statistically significant association between the two syndromes in univariate and multivariable models. Fatigue and cognitive impairment showed distinct age distributions: cognitive impairment increases with age while fatigue is commonly reported in the younger age group. While cognitive impairment was mostly associated with low sociodemographic status, fatigue showed strong associations with psychiatric comorbidity and early COVID-related neurological involvement. Fatigue occurs shortly after the acute phase with gradual improvement over time, whereas the onset of dementia and cognitive impairment may be delayed by months after infection. Thus, these fatigue and cognitive impairment are two

distinct sequelae of post-acute sequelae of COVID-19 with different underlying pathogenesis [53].

Sleep disturbances and mood/ anxiety disorders

The development of neuropsychiatric complications including depression, anxiety, post-traumatic stress disorder and sleep disturbances may be attributed to social confinement, isolation, trauma during acute infection. The risk of these complications was greater in women. The patients in confinement for a moderate duration of 3 to 6 weeks were at greater risk of insomnia as compared to those with no confinement or confinement for longer duration greater than 7 weeks. This may be attributed to the immediate stress response due to mandatory confinement followed by people adapting to it [54].

The adult population was at increased risk of developing mood and anxiety disorders. In contrast, children were at greater risk of seizures, nerve, nerve root and plexus disorders. Also, there was increased risk of psychiatric and neurological complications associated with the delta variant while no such association was seen with the omicron variant [55].

Neurodegenerative disorders

The cytokine release is responsible for neuroinflammation, which creates an environment favorable for cognitive decline. In COVID-19 patients with ventilation-induced hypercapnia, NLRP3 inflammasome mediated inflammation has experimentally shown to induce accumulation of amyloid β. The interleukin induced regulation of phosphokinases and phosphatases in COVID-19 patients leads to accumulation of neurofibrillary tangles. Both these mechanisms lead to pathogenesis of Alzheimer's disease [55].

The cytokine release is also responsible for α-synuclein seeding, an underlying factor in pathogenesis of Parkinson's disease. Ageusia and anosmia, the two key symptoms of COVID-19 are also prodromal features of Parkinson's [56].

Alteration in brain structure with COVID-19

A study evaluated the brain scans and cognitive scores of patients of COVID-19 along with healthy controls. The cases had a greater loss of grey matter thickness in the para-hippocampal gyrus and orbitofrontal cortex, the area associated with olfactory sensation along with decreased brain volume. There was a decline to perform complex tasks, which was detected on brain scans as atrophy of crus II in cerebellum [56,57].

Conclusions

Although the respiratory tract is the predominant target of SARS-CoV-2, the neurological manifestations can also cause significant morbidity and mortality. The neurological symptoms in COVID-19 range from mild symptoms like headache, ageusia and anosmia to severe life-threatening symptoms like stroke and encephalopathy. The Long Covid Research Initiative has developed a research program to evaluate the effect of SARS-CoV-2 virus on the immune system along with its impact on nerve signaling, cognitive function and coagulation [58].

However, there are certain limitations pertaining to the diagnosis of PASC. Firstly, there is a lack of consensus whether a previous confirmed COVID-19 report or serological evidence of infection should be a pre-requisite for diagnosis. Also, there is no consensus regarding the time frame for PASC. The Centers for Disease Control and Prevention proposed a cut off of 4 weeks after acute infection. However, the National Institute for Health and Care Excellence and WHO defined Ongoing Symptomatic COVID as 4-12 weeks post infection and post COVID-19 syndrome as persistence of symptoms beyond 12 weeks.

Another limitation is that whether neurological sequelae in intensive care unit patients should be included in the neurological manifestations of PASC.

Contributions

- Sana Ahuja: Conceptualization, design, literature search, manuscript preparation.
- Sufian Zaheer: Conceptualization, methodology, writing, review and editing, guarantor.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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