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Review Article

COVID -19: A REVIEW ON POST COVID- 19 MANIFESTATIONS AND COMPLICATIONS

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Abstract:

COVID -19 (corona virus disease 19) or SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) is an emerging infectious disease spreading worldwide. Symptoms may varies person to person. In some patients due to the increased release of inflammatory cytokines disease may progress to pneumonia, respiratory failure or even death. Studies identified the entry of virus to the respiratory mucosa is through the angiotensin receptor 2 (ACE2). Coronaviruses are mainly divided into four types based on the structural genomics as α, β, γ, and δ. Middle east respiratory syndrome corona virus(mers-cov) and severe acute respiratory syndrome 2(sars-cov2) comes under beta coronaviruses. As COVID-19 is an ongoing crisis faced by the world, knowledge on various aspects of COVID -19 is essential. Recent studies evinced the post covid-19 complications following acute covid-19 infections. A multitude of complications are faced by patients after acute infectious period of COVID-19, for instance neurological, respiratory, cardiovascular, hematological, gastrointestinal and ophthalmological manifestations and complications. Almost all systems are affected by SARS-COV2 virus hence post covid follow-up checkup should be encouraged for all covid -19 recovered patients. The emergence of post covid care centres or clinics should be promoted in order to reduce the subsequent sufferings accompanied with COVID-19 recovery. This review summarises the various post covid-19 manifestations and complications.

Keywords: Covid -19, SARS-COV-2, Post covid -19 complications

Introduction:

COVID -19 (corona virus disease 19) or SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) is an emerging infectious disease spreading worldwide. Coronaviruses which is a type of beta coronavirus is an “enveloped positive sense RNA viruses” having “spike like projections” on its surface which resembles a crown during microscopic evaluations and so called as coronavirus. The virus spreads by the inhalation of droplets produced during coughing and sneezing by the infected patients or touching the contaminated surfaces by virus and then moving to eyes nose or mouth. Studies suggest that greater viral loads are present in the nasal cavity than in throat. Incubation periods usually varies from 2 to 14 days. Studies identified the entry of virus to the respiratory mucosa is through the angiotensin receptor 2 (ACE2)[(1)].

The symptoms are sore throat, fever, cough, breathlessness, diarrhoea, nausea and vomiting, headache, fatigue, myalgia. Symptoms may varies person to person[(2)]. In some patients due to the increased release of inflammatory cytokines like il(2,7,10), G-csf , ip10, mcp1, mip1a, and TNF α disease may progress to pneumonia, respiratory failure or even death. Neurological manifestations of covid-19 in CNS includes encephalopathy, epilepsy, encephalitis, acute myelitis, headaches, dizziness and in PNS hyposmia, neuralgia guillian barre syndrome, dysosmia ,dysgeusia are found [(3)].Cardiovascular complications are also linked with covid-19 which includes myocardial injury ,myocarditis, acute myocardial infarction, acute heart failure and cardiomyopathy, dysrhythmias, deep vein

thrombosis[4]. Hematological complications are lymphopenia, blood hypercoagulability, increased d-dimer levels, prolongation of pt (prothrombin time) and aptt (activate partial thromboplastin time), thrombocytopenia and disseminated intravascular coagulation (dic)[5].Multiple organ dysfunctions is also a complication of SARS COV-2. Diagnosis can be done by real-time reverse-transcriptase-polymerase chain reaction (RRT-PCR) and rapid antigen test using throat swab or nasopharyngeal swab. Other laboratory tests includes WBC count to check lymphopenia, elevated CRP, ESR prothrombin time, creatinine, d-dimer, CPK and LDH. Since there is no approved treatment, preventive measures are taken like wearing face mask and practising hand hygiene with soap or sanitizer [1].

PATHOPHYSIOLOGY

Coronaviruses are mainly divided into four types based on the structural genomics as α, β, γ, and δ. Alpha and beta types only infects mammals. Middle east respiratory syndrome corona virus(mers-cov) and severe acute respiratory syndrome 2(sars-cov2) comes under beta coronaviruses. The coronavirus after infecting the host consist of several steps like attachment, membrane fusion, biosynthesis, maturation and release.

First step is attachment, here the virus enters host cells by the process of endocytosis or by membrane fusion(penetration). Then viral materials will be released inside the host cells and viral RNA goes to the nucleus for replication. Viral proteins are made by viral mrna and the process is called biosynthesis followed by maturation where new viral particles are produced and released. Spike (s), membrane (m), envelop (e), nucleocapsid (n) are the structural proteins of coronaviruses [6]. The receptor for coronavirus was identified to be angiotensin converting enzyme 2 (ACE2) which is mainly found in lungs (lung epithelium), heart, kidney, bladder and ileum [7]. The virus after binding to the host protein, protease cleavage takes place in spike protein by two step sequential process. The s1 and s2 subunits stay non covalently bounded after undergoing cleavage at s1/s2 cleavage site. When membrane is tied up with s2 subunit during pre-fusion stage, s1 subunit is responsible for stabilisation. Followed by s′2 site cleavage and for membrane fusion ,spike will be activated which is irrevocable conformational change[8]. The distinctive feature of SARS-COV 2 is the presence of furin cleavage site also called "RPPA" sequence in the vicinity of s1/s2 site. S1/s2 site is also imperil to cleavage by transmembrane protease serine 2 (tmprss2) and cathepsin l[9]. The highly pathogenic stage of virus is caused by furin's ubiquitous expression [6].

SARS -COV-2 AND HOST RESPONSE

When antigen enters the cells through dendritic cells(dc's) and macrophages, T-cell responses are initiated The antigen presenting cells passes the draining lymph nodes to expose the viral antigens to T-cells. Here $CD4^+$ t-cells and $CD8^+$ T-cells plays a key role . $CD4^+$ T-cells actuates the b cells for the generation of viral specific antibody, meanwhile $CD8^+$ T-cells can slaughter infected cells. The severely ill patients were found to have lymphopenia, high increase in proinflammatory cytokines such as interleukin (il-6, il-10), monocyte chemoattractant protein 1 (mcp1), granulocyte-colony stimulating factor (G-CSF), tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)1α.

Nkg2a (nk group 2 members) is the other marker for exhaustion of T-cells . In this condition $CD4^+$ cells and $CD8^+$ cells is highly activated. The process, exhaustion of T-cells leads to disease progression . Another important response seen during corona virus infection is GM-CSF (granulocyte-macrophage colony-stimulating factor) expression which aid to distinguish innate immune cells and elevate functions of T-cells but it may leads to tissue damage when excess. Studies proved that the lung epithelial cells which are infected by virus produces il-8 and il-6, however il-8 is a chemoattractant agent for T-cell and also for neutrophils .in severe covid -19 patients ,a high amount of inflammatory cells was found in lungs .although among innate immune cells, neutrophils causes deleterious effects and cause lung injury . The presence of cytotoxic t cells ($CD4^+$ cells) presumably seen in severe patients and when these cells tries to kill the virus lung injury can be occurred. Elevated presence of il-6 can hasten the progress of systematic inflammatory response. Not only respiratory symptoms are prior but pulmonary embolism ,thrombosis can also be occurred during severe diseased conditions and can be diagnosed by

checking increased d-dimer and fibrinogen levels[6]. Coagulopathy, cardiac dysfunctions, neural injury are the other complications. Together the impaired acquired immune responses along with ungovernable inflammatory innate responses to the coronavirus causes cytokine storm which can cause harm to the patients suffering from covid-19. Treatment options for cytokine storm includes Corticosteroids, Hydroxychloroquine, Tocilizumab and Anakinra[10].

NEUROLOGICAL MANIFESTATION AND COMPLICATIONS

The SARS -COV2 binds with ACE-2 receptors and it further activates pathogen recognition receptors (prrs) mediated innate immune system activation and stimulate cytokine release and cause hyperinflammation mediated injuries. When the virus binds to the ACE2 receptors it also causes ACE-2 downregulation. Then cytokine's reaches cerebral microvasculature from the periphery. Then endothelial autoregulation impairment, disruption of BBB, cerebral hypoperfusion and culminated to neuroinflammation [11].

Neurological symptoms of SARS COV-2 are classified as 3 categories :PNS manifestations are vision impairment ,nerve pain ,dysosmia, dysgeusia. CNS manifestations are "dizziness, headache, impaired consciousness, ataxia, seizure, cerebrovascular disease". In skeletal muscles, manifestations of skeletal muscle injuries are common [12].

Post-COVID-19 Neurological Syndrome is an emerging complication of COVID -19. Possibly systemic inflammation, peripheral organ dysfunction (liver, kidney, lung), cerebrovascular changes and direct viral encephalitis are the conditions which causes CNS neurological manifestations of COVID-19[13] . Systemic inflammation give rise to cognitive decline and neurodegenerative disease[14]. Studies suggest that patients suffering from severe sepsis may experience hippocampal atrophy in future[15].

Guillian-Barre syndrome (GBS)

Guillian-Barre syndrome (GBS) is an immune mediated polyradiculoneuropathy where symptoms such as cranial nerve or limb weakness, sensory symptoms, dysautonomic symptoms and loss of deep tendon reflexes. The symptoms occurs because of axonal damage to the peripheral nerve demyelination . Culminations from studies showed GBS and Bickerstaf's encephalitis has been specified as a post infectious complications of other types of coronavirus which is almost identical to SARS-cov-2 however further studies are essential to correlate the pathophysiologic relations of COVID-19 and GBS [16].

Parkinson's disease

At glance dysosmia and dysgeusia is an usual symptom of COVID-19 so perhaps in future there is a chance for the generation Parkinson's disease. However more studies are essential to confirm the correlation of pathogenesis of parkinson's disease and COVID -19[17].

Refractory status epilepticus (RSE)

Occurrence of seizure has been emerged as a symptom during the acute infectious stage of covid 19 in many cases and ought to be due to cytokine storm and CNS viral invasion. In some case studies refractory status epilepticus (RSE) is reported in recovered patients from COVID-19. Post infectious inflammatory responses are found to be a reason for the occurrence of post covid-19 seizures hence due to the elevated systemic inflammatory markers[18].

RESPIRATORY MANIFESTATIONS AND COMPLICATIONS

Pneumonia -Pulmonary Fibrosis

The chest imaging of covid -19 pneumonia patients revealed "multiple bilateral peripheral opacities'' and in CT scan some regions exhibits consolidation and ground-glass opacification.

Even though most of the covid -19 patients recovered fully, certain cases of severe acute respiratory distress syndrome persists to be endured in a hypoxemic state. Chest radiography resulted fibrotic changes like "bronchiectasis, architectural distortion and septal thickening'' which is akin to other fibrotic lung diseases[19]. During the inflammatory phase of acute respiratory distress syndrome (ARDS)Dysregulation and release of matrix metalloproteinases occurs and leads to epithelial and endothelial injury and fibroproliferation .vascular dysfunction is also found

which shifts ARDS to fibrosis meanwhile vascular endothelial growth factors, cytokines (IL-6),TNF alpha is released [20].

The patients with severe disease even after discharge from hospital had impairment of the transfer factor of the lung for carbon monoxide (tlco) ie, low level of tlco[22] . In severe cases tlco/alveolar volume (Kco) is also found when compared with mild to moderate covid -19 cases probably due to pulmonary vasculopathy[23].

CARDIOVASCULAR MANIFESTATIONS AND COMPLICATIONS

Many cardiovascular complications are followed by COVID -19. The most fatal complication is cardiogenic shock. Myocarditis with myocardial injury is a complication presumably due to the increased level of serum troponin level and for such patients ECG variations for instance inverted T wave, PR segment depression and ST segment elevation are found[23,24]. Acute myocardial infarction is suspected in COVID 19 patients which is a consequence of severe inflammation and hyper coagulability [25]. Dysrhythmia, usually sinus tachycardia is also associated with elevated troponin level. COVID- 19 patients is also prone to an elevated risk of venous thromboembolic events (vtes) due to severe systemic inflammations, hypercoagulability and multiple organ dysfunctions [25].

Heart failure and cardiomyopathy is also manifested in COVID-19 patients. During the acute infection, an elevated release of cytokines is presumably considered as a major cause of cardiomyopathy. Following the preceding effects generation of prothrombotic state is seen in the acute phase which later progresses to pulmonary embolism, thrombus formation, and coronary artery disease is exacerbated [26,27].

Vascular complication occurring during post COVID -19 phase is ought to be due to the secondary effects of cytokine storm and severe systemic inflammation[28]. These effects will give rise to a series of complications like endothelial dysfunction, generation of atherosclerosis, instability of plaque, myocardial infarction, increased risk of venous thromboembolic events and hypercoagulability[27,28].

HEMATOLOGICAL MANIFESTATIONS AND COMPLICATIONS

Hematological abnormalities such as lymphocytopenia, thrombocytopenia, and leukopenia was found in laboratory evaluations of COVID-19 patients. Studies concluded that there is a correlation among lymphopenia and burgeoning of acute respiratory distress syndrome (ARDS) .Elevated neutrophils and declined lymphocytes is the baseline cause of fatal effects of ARDS[29]. Further studies implied CD4+ helper and regulatory T-cells functions were affected by SARS COV -2. Initially hyperactivation of these cells were found which later progressed as an expeditious exhaustion of cytotoxic CD8+ T-cells. Studies showed that patients with myocardial injury is having elevated leukocyte, reduced lymphocyte and platelet counts also patients with elevated troponin-T levels is having leukocytosis ,elevated neutrophils and reduced lymphocytes. A peak platelet to lymphocyte ratio resulted from a more prominent cytokine storm and platelet activation[30].

Blood viscosity is increased due to the release of peak quantity of inflammatory mediators and due to the treatment with hormones and immunoglobulin in critically ill patients. Blood hypercoagulability is a major complication after COVID 19. Biomarkers like serum procalcitonin and ferritin may be elevated. Surge of D-Dimer levels in the patients increases the severity of disease also leads to worsening of disease. Some other coagulation abnormalities are also found including PT and aptt prolongation, elevated fibrin degradation products via severe thrombocytopenia give rise to disseminated intravascular coagulation(DIC). There is also a high risk of venous thromboembolism, and subsequently prolonged pharmacological treatment is necessary with low molecular weight heparin for the patients even after discharge from hospital [30].

OPHTHALMOLOGIC COMPLICATIONS

SARS-cov-2 infection via immune mediated reactions affects the eye vasculature. COVID -19 survivors may have impaired retinal vascularization and should be assessed following post COVID-19 phase. Macula as well as optic nerve evaluations should be done to check the degree of macula-optic

nerve vascular impairment [30].

GASTROINTESTINAL MANIFESTATIONS AND COMPLICATIONS

GIT symptoms suffered by COVID-19 patients includes diarrhoea, vomiting and nausea, pain in abdomen and gastrointestinal bleeding. COVID -19 viral infections causes post-infectious gastrointestinal disorders. Drugs which are used to symptomatically treat COVID-19 like hydroxychloroquine, antibiotics and antivirals may have the potential to cause post covid -19 gastrointestinal complications [30,31].

POST COVID 19 FATIGUE

Fatigue is the most tenacious symptoms found after the acute infectious phase of COVID -19. Persisting symptoms may last up to 1 year after COVID 19. The most susceptible ones are those patients with existing neurological problems meanwhile the accurate mechanism is unknown[32]. Central factors which contributes to the post covid -19 fatigue is probably due to the penetration of SARS COV -2 to the CNS which may cause changes in serotonin and dopamine levels, demyelination, neuronal excitability and inflammations[33,34]. Psychological factors involves the post-traumatic stress disorders, stress, fear, anxiety, confusion, depression. These factors may prolong the recovery from fatigue after COVID-19. Peripheral factors includes the after effects of viral invasion to tissues like skeletal muscle which causes myopathy. Collectively these three factors contributes to the conditional dependency which collectively includes tasks performing, environmental variations and physical and mental ability of the patients. Patients with other co morbidities already have fatigue presumably when they are affected with COVID-19 there is a raised possibility for persisting fatigue when compared with patients without any co morbidities[32]. As a conclusion some patients may suffer from Chronic fatigue syndrome (CFS) after recovering from COVID-19.

Conclusion

As COVID-19 is an ongoing crisis faced by the world, knowledge on various aspects of COVID -19 is essential. Only symptomatic treatments are available and Since there is no approved pharmacological treatment against SARS COV-2 necessary measures should be taken to prevent covid -19 infections as always "prevention is better than cure''. Recent studies evinced the post covid-19 complications following acute covid-19 infections. The emergence of post covid care centres or clinics should be promoted in order to reduce the subsequent sufferings accompanied with COVID-19 recovery. A multitude of complications are faced by patients after acute infectious period of COVID-19, for instance neurological, respiratory, cardiovascular ,hematological ,gastrointestinal and ophthalmological manifestations and complications. Almost all systems are affected by SARS-COV2 virus hence post covid follow-up checkup should be encouraged for all covid -19 recovered patients.

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