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Autonomic nervous system involvement in COVID 19 and risk of Sudden cardiac death

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ABSTRACT:

The acute SARS CoV 2 infection causes increased metabolic demand with reduced cardiac reserve, tachypnoea, acidosis, hypoxia causing deleterious effects on cardiac myocytes. Since its heightened sympathetic state these patients are more prone for malignant arrhythmias. The central nervous system involvement of MERS-CoV is mostly caused by the autoimmune reaction against viral antigens rather than viral infection itself. Although coronaviruses can infect the autonomic center in the brainstem, potentially contributing to cardiovascular and respiratory failure, the direct effect of SARS-CoV2 on the autonomic nervous system is not well known yet. The purpose of this review is to emphasise the involvement of autonomic nervous system (ANS) which is an integral part of our human body to adapt for the stressful environment like COVID 19 infection.

Keywords: COVID 19, Sympathetic and Parasympathetic system, Arrhythmias

Introduction

In December 2019, the novel corona virus related disease named Covid 19 caused by SARS-Cov2 and identified first in Wuhan, China had rapidly spread to more than 220 countries causing a pandemic situation. At present, on May 2021 Covid 19 had affected more than 170 million people and with varying case fatality rate of 4 % ranging from (0.1% to 20%).[1] In the past two decades similar human corona viruses (HCoV) like SARS CoV and MERS virus had caused epidemics similarly like Covid 19 which belonged to same group of viruses. This group of viruses initially affects upper respiratory tract and causing severe pneumonia, acute respiratory distress syndrome leading to severe morbidity and mortality.[2]

Recently, the pandemic of covid 19 involved various countries, gender differences, elderly individuals and different population among the world and led to the understanding of pathophysiological mechanisms causing multiple organ system involvement and mortality.

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Lessons learnt from the past

Till date there are 7 different strains of HCov identified , out of them 4 (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) causes mild upper repiratory tract infections which are usually self limiting infections.[3] However, Desforges et al have reported that the HCov can cause short term and long term sequelae in neurological disorders such as encephalomyelitis and multiple sclerosis.[4] So it clearly shows that the HCov have the properties of neuroinvasive and neurotropic properties spreading via hematogenous and retrograde neuronal routes.

According to the data from Chinese studies SARS-Cov viruses were identified in the brain autopsy of deceased patients.[5] It is frequently found in the cerebrospinal fluid (CSF) of patients of diagnosed SARS patients. SARS also caused muscle weakness, elevation of creatinine kinase, critical illness related polyneuropathy and late onset myopathy.[6] Chronic post SARS syndrome and autonomic dysfunction causing malaise and weakness were reported. In contrast to covid 19 the olfactory nerve involvement is identified in the late stage of the disease.

The central nervous system involvement of MERS-CoV is mostly caused by the autoimmune reaction against viral antigens rather than viral infection itself.[7] Saad et al conducted a retrospective study which showed that the patients with MERS had confusion and seizures in 25 % and 8.6 % patients respectively.[8] Arabi et al reported a case series that patients with a diagnosis of acute disseminated encephalomyelitis, acute bilateral non-occlusive stroke due to encephalitis and MERS-CoV vasculopathy.[9] Intracerebral haemorrhage due to thrombocytopenia, disseminated intravascular coagulation and platelet dysfunction was very rare due to MERS-CoV infection.[10] The triple antiviral treatment used for MERS-CoV infection (pegylated interferon 2alpha, high dose ribavirin and oral ritonavir/lopinavir) perse may lead to neurological complications.[11]

It is very clear that in addition to non specific symptoms like fever, cough, myalgia, nausea, headache, vomiting, diarrhea some patients can present with dizziness, confusion and with seizures.[12] Anosmia and hypogeusia are the cardinal symptoms that makes early diagnosis of Covid 19 infection via direct olfactory bulb invasion. The ACE II receptor serves as a receptor for SARS-CoV2 and it is widely distributed in heart, lung, intestines, kidney, testis, nose, and mouth[17] and glial cells in nervous system.[13]

Covid 19 and autonomic nervous system

Although coronaviruses can infect the autonomic center in the brainstem, potentially contributing to cardiovascular and respiratory failure, the direct effect of SARS-CoV2 on the autonomic nervous system is not well known yet. The patients with cardiovascular disease like coronary artery disease, heart failure, hypertension, diabetes, cerebrovascular disease and other comorbidities like chronic airway disease, chronic kidney disease, cancer are more susceptible and associated with worse outcomes.[14]

The acute SARS CoV 2 infection causes increased metabolic demand with reduced cardiac reserve, tachypnoea, acidosis, hypoxia causing deleterious effects on cardiac myocytes. Since its heightened sympathetic state these patients are more prone for malignant arrhythmias.[15]

The increased sympathetic activity may lead to stress induced cardiomyopathy frequently reported during this pandemic.[16] The post traumatic stress event usually occuring after major disasters or serious medical condition including the pandemic might be a significant risk factor for cardio vascular diseases, stroke and thrombotic diseases.[17] The autonomic imbalance leads to hyperglycemia which is an independent risk factor for Covid 19 patients and also hypokalemia due to increased adrenaline(beta agonist) , which is a predisposing factor for arrhythmias.[18] In patients with COVID-19, hyponatremia can be an early or isolated finding.[19]

Hyponatremia has been ascribed to inappropriate secretion of ADH. It is unknown whether hyponatremia is an independent predictor of outcome in COVID-19. [20]

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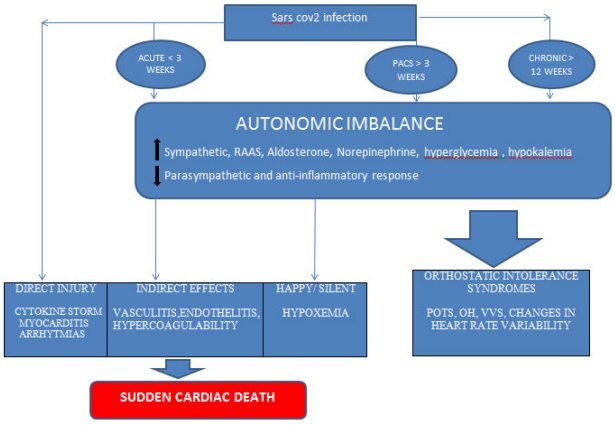
It also causes increased heart rate, abnormal variability in heart rate, and QTc prolongation. The QTc prolongation may be non specific or may be due to chloroquine or hydroxychloroquine.[21] The increased sympathetic activity might be a predisposing factor for endothelial injury and thrombotic events.[22]

Importantly, the cytokine storm (IL 6, IL 10, TNF alpha) caused by SARS-CoV 2 infection may trigger endothelial injury and vascular inflammation.[23]

Finally the counter regulatory component of autonomic system is parasympathetic cholinergic system, which gets activated by infection and inflammation. [24] Activation of the vagal anti-inflammatory reflex results in the inhibition of cytokine synthesis by macrophages of the mononuclear phagocytic system including resident and circulating macrophages. These changes are observed in many tissues including the lungs, heart and brain. The cytokine storm of Covid 19 infection is the sudden transition from compensated to decompensated state requiring mechanical ventilation. So these patients with parasympathetic withdrawal due

Figure 1. SARS-CoV2 and the autonomic nervous system –risk of sudden cardiac death



PACS- Post acute covid syndrome, POTS-postural orthostatic tachycardia syndrome, VVS-vasovagal syncope, OH-Orthostativ Hypotension

to comorbidities, may be at higher risk of developing sudden increases in cytokine release due to the lack of a fully functional neuro-vagal anti-inflammatory reflex.[25] Some reports suggested that the vagal nerve stimulation might be helpful in restoring autonomic imbalance and reducing inflammation.[26]

During the pandemic, the patients who recovered from acute Covid 19 infection were presented with persistent symptoms like cardiopulmonary and neurologic complaints including fatigue, palpitations, chest pain, breathlessness, and dysautonomia.[27]

Researchers named it as post acute covid syndrome (PACS) or post acute sequelae of SARS-CoV2 infection(PASC) or Long Covid with persistent symptoms after 3 weeks and Chronic Covid with symptoms after 12 weeks.[28] Numerous studies showed that the patients discharged from hospital had fatigue(53 %) at 2 months and fatigue (more than two third) after 4-8 weeks. These patients have a wide variety of orthostatic syndromes like postural orthostatic tachycardia syndrome, vasovagal syncope, orthostatic hypotension.[29]

Risk of Sudden cardiac death (SCD): Even though the prevalence of ST elevation myocardial infarction(MI) decreased 20 %, the incidence of type 1 MI (plaque rupture or erosion) and type 2 MI (oxygen supply/demand) were reported 0.9%–11% in Covid 19 infections.[30] Elevated cardiac troponin (cTn) levels were rare in COVID-19 survivors with an uncomplicated course (1%–20%), common in severely ill patients (46%–100%), and nearly universal in the critically ill (ie, requiring intensive care or mechanical ventilation) and non survivors.[31] It clearly indicates the increased cTn levels predicts mortality.[32] Data from the hospitalised patients with Covid 19 infection shows acute heart failure (3%–33%), cardiogenic shock (9%–17%), ventricular dysfunction (left ventricular [10%–41%], arrhythmias (9%–17%), venous thromboembolism (23%–27%), [33] and arterial thrombosis

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secondary to viral-mediated coagulopathy. In a systematic review comprising 199 patients from 34 acute or postrecovery cardiac MRI studies in patients with COVID-19, the diagnoses included myocarditis in 40.2%, myopericarditis in 1.5%, Takotsubo in 1.5%, ischemia in 2.5%, and dual ischemic and non ischemic changes in 2.0%.[34]

Arrhythmia related to sudden cardiac death is caused by direct viral cytopathic effect and involvement of host and viral factors like ion channelopathies, oxidative stress, inflammation, altered intracellular signalling, myocardial edema and ischemia. These structural changes leads to abnormal calcium handling and down regulation of potassium channels, potential risk for early or delayed depolarisation or re-entry.[35] Arrhythmias related to myocardial scar occurs during post inflammatory stage.[36] Fatal arrhythmias in COVID-19 may also result due to hypoxia because of, direct viral lungs involvement, cardiac dysfunction, or severe systemic inflammatory state, electrolyte derangements, intravascular volume imbalances, and drug side effects. Hypoxemia which frequently occurs in Covid 19 patients leads to reduced electrical coupling and anisotrophy causing proarrhymthic state.[37] Bradyarrhythmia, asystole and pulseless electrical activity are also observed in the hospitalised patients with Covid 19.[38] The hyper inflammatory state which causes endothelial injury leads to activation of coagulation system, prolonged bed stay aggravating the risk of thromboembolic phenomenon. Between 21% and 69% of critically ill patients with COVID-19 present with venous thromboembolism leading to aute pulmonary embolism (most common) which is an aggravating factor for sudden cardiac death. The drugs like chloroquine/hydroxyl chloroquine used during the initial pandemic times had risk of QTc prolongation and arrhythmias. The incidence of QTc prolongation varies 7% to 36% in the hospitalised patients with Covid 19. An observational study showed that among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.[39] In another cohort study the treatment with chloroquine/hydroxychloroquine ± azithromycin was not associated with instances of Torsades de pointes or arrhythmogenic death. Although use of these medications resulted in QT prolongation, clinicians seldomly needed to discontinue therapy.[40] So that the incidence of drug induced QTc prolongation and the SCD is low.The other predisposing causes that may lead to SCD is depends on case to case basis. The proposed causes are consumption coagulopathy/disseminated intra vascular coagulation, coronary artery dissection, uncovering of channelopathy (hypoxia and electrical imbalance) and cardiac tamponade.[41]

Happy hypoxemia or silent hypoxemia: The ACE 2 receptors are highly expressed in the tongue and olfactory bulb, through which SARS-CoV 2 enters nucleus tractus solitaries (NTS) which is a relay station of taste pathway located on dorsal medial medulla.[42] It also receives visceral afferents from almost all organs in the body through the vagus nerve by which it plays an important role in cardiovascular function, respiration, gastrointestinal mobility, and immune modulatory function. It receives the afferent pathway from carotid receptors located on carotid artery bifurcation which is responsible for increase in respiratory rate and vasoconstriction in response to hypoxia. Since the COVID 19 patients are hypoxic there is ineffiecient afferent response to hypoxia because of the virus induced damage of NTS causing no sensation of dyspnoea inspite of low patial pressure of oxygen. It plays a significant role in the Covid 19 patients with SCD.

Conclusion

The Covid 19 pandemic had significant impact on health care, economic and stress factors world wide. After a small decline of cases in summer 2020, positive rates have risen up in December and finally we are in the second wave of the pandemic. Since we hypothesized about the involvement of ANS in the acute, post acute Covid syndrome and chronic Covid and the risk of SCD in these patients, so the early identification of the Autonomic function testing is essential for quantification, and localization of autonomic dysfunction of Covid 19 patients with comorbidities, and are relevant to diagnosis, prognosis, clinical management of patients to improve their quality of life and reducing sudden cardiac death. Recently the American autonomic society published the guidance of autonomic testing in the safe environment.

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