Narrative Review

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A Survey on Cardiac Complications of COVID-19 in Infants

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ABSTRACT

Congenital heart disease (CHD) may have serious effects on the course of COVID-19. Limited data were available on CHD in neonates with COVID-19. This study aimed to review the cardiac complications in neonates infected with COVID-19. Some studies showed that myocardial injury in adult patients is often correlated with a fatal outcome. But, scientific evidence in infants is rare, although several reports were published with the description of cardiac involvement in COVID-19 pediatric patients. In these young subjects, a background of surgically treated CHD seems to be a predisposing factor. Numerous studies showed Multisystem inflammatory syndrome in children (MIS-c) is a deadly demonstration of COVID-19 with cardiac involvement. The underlying pathophysiology of COVID-19-associated cardiovascular complications is not fully understood, although direct viral infection of the myocardium, systemic inflammatory response, coagulation abnormalities and thrombosis and hypoxia have been suggested as possible mechanisms of cardiac complications. It seems COVID-19 can affect different parts of the heart; however, the myocardium is more involved. The mechanisms of pathogenesis of cardiovascular implications in adults and infants are similar but CHD and MIS-c in infants are more important. Further studies on the effects of COVID-19 on the neonatal cardiovascular system are needed.

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV2) infection, the first pandemic of the time, makes the new coronavirus infection (COVID-19). That was first begun at Wuhan in 2019. The disease had a fast spread all over the word with recurring peaks of the epidemic and considerable fatality worldwide.[1] COVID-19 main targets are airways and lungs and the most common manifestations of the infection are described as fever, fatigue, and dry cough.[2,3] But this viral epidemic has been published to be correlated with a broad spectrum of cardiac manifestations and appearances of subclinical myocardial injury, myocarditis, arrhythmias, cardiovascular and pulmonary thrombosis.[4] COVID-19 seems to be less threatening in pediatric cases and associated signs milder than in adults.[5] The method through which pediatric appears less sensitive to acute infection induced by COVID-19 has still to be explained. According to one theory, the angiotensin-converting enzyme 2 (ACE-2) as a binding protein for COVID-19 in pediatrics is not as effective as in adults, and therefore COVID-19 is less dangerous.[6,7] The most frequent presentations in pediatric are moderate fever, cough, rhinorrhea, and sore throat. Gastrointestinal manifestations similar vomit and diarrhea are probable as well.[8,9] The lower prevalence of COVID-19 in children, besides the higher numbers of mild and asymptomatic cases, continues to provide difficulties in determining proper prevention and treatment methods. The large majority of clinical patients of SARS-COV2 in pediatric are mild, but few cases have developed difficulties such as MIS-c in children, which often manifests with severe cardiac symptoms needing intensive care.[10] Although all age groups are sensitive, infants below one year displayed the highest proportion of acute and dangerous patients, almost 10.6% compared to other age groups recommending that infants may be at higher risk of critical respiratory failure.[6] Furthermore, the existence of CHDs or any other comorbidity may have a severe influence on the development of this disorder in newborns and early infancy. There is only limited data describing the effects of COVID-19 on the pediatric population. Also, evidence is inadequate around the impact of COVID-19 in children with heart disease particularly in the age below one year.[11]

A few studies reported pediatrics with CHD and SARS-COV2, and as a result the influence of the virus on this special patient group is not apparent. So, knowing the mechanisms of SARS-COV2–mediated cardiac disorder may affect advances in the therapy and control of these cases.[12] In this study, we reviewed the implications for infants with the cardiac disorder in general and CHD in particular, and attempted to define the underlying mechanisms responsible for SARS-COV2-associated myocardial injury. We reviewed the cardiac complications in neonates infected with COVID-19.

Types of cardiac complications of COVID-19

Myocarditis: Myocarditis is an inflammatory illness of the myocytes presents with a spectrum of symptoms.[13] It is described as proof of high troponin levels with at least one rate up the 99% above the reference limit in the lack of myocardial ischemia.[14] Myocardial damage was another problem usually described in patients with severe SARS-COV2 disease. Virus infection has been broadly characterized as one of the most frequent causes of myocarditis. Direct viral destruction of cardiomyocytes, a hyperinflammatory condition, and cytokine storm, that ordinarily happen in severe cases, have been proposed as the principal drivers of severe myocardial damage and myocarditis.[12] Raised troponins during hospitalization were also correlated with an enhanced risk of needing ventilation, lethal ventricular arrhythmias, and a 59.6% fatality risk.[15] SARS-CoV-2 looks to affect the myocardium

and cause myocarditis. Myocardial damage is possibly correlated with infection- associated myocarditis and/or ischemia. Sporadic autopsy subjects propose infiltration of the myocardium by interstitial mononuclear inflammatory cells, particularly in the subjects of fulminant myocarditis. Though the realization that SARS-COV2 may induce acute myocarditis helps early diagnosis and feasible prevention of myocarditis- associated fatality, lack of a recognizing of the mechanisms by which COVID-19 contributes to myocarditis and cardiac injury prevents accurate control of this situation.[12]

Heart Failure: Heart failure (HF) was identified in 23% of 191 COVID-19-positive inpatients in China.[16] As heart failure is most frequently due to intensification of previous left ventricular dysfunction or new cardiomyopathy must be more explained. Cardiac pericytes with a high expression of ACE2 might work as the target cardiac muscle cell of COVID-19. Cardiac Pericyte damage due to virus contamination may lead to capillary endothelial cell dysfunction, causing microvascular dysfunction. A higher level of ACE2 expression was observed in patients with primary heart failure on both mRNA and protein levels, suggesting that these subjects may have a greater risk of heart attack and serious illness if infected by the virus. In patients with heart failure, the rate of the expansion of the small pulmonary veins was higher, and lung lesions remarkably improved after efficient anti-heart failure therapy. There are more complications with rounded morphology in SARS-COV2.[17] Moreover, those with underlying cardiac co-morbidities, for example chronic hypertension, were more probable to develop HF. The HF patients were determined to be at a higher risk of thromboembolic situations, acute respiratory distress syndrome (ARDS), severe hypotension, and death. Symptoms and signs of cardiovascular problems, such as dyspnea and chest pain, may have an important overlay with SARS-COV2. Additionally, cardiovascular problems have been noted to happen usually through the illness. As such, cardiovascular problems should always be examined particularly in more severe SARS-COV2 cases, such as those needing hospitalization.[14]

Arrhythmias: Arrhythmias and unexpected cardiac arrest are usual demonstrations of COVID-19. Heart palpitations have been stated to be the main manifestation presentation of SARS-COV2 in cases without fever or cough.[18] Though, the specific participation of SARS-COV2 to cardiac arrhythmias continues doubtful given that arrhythmias, including fibrillation and, atrial and ventricular tachycardia, can be triggered by myocardial damage or other systemic causes including sepsis, fever, hypoxia and electrolyte irregularities.[4] It was mentioned to happen more commonly in patients needing ICU admission than those who did not.[14] The influence of SARS-COV2 on cardiac arrhythmias results from myocardial damage and subsequent cardiac dysfunction. Extra attention would be arrhythmia monitoring and whether a need for an implantable cardioverter-defibrillator or wearable cardioverter-defibrillator after discharge.[17] The progress of severe malignant arrhythmias, including ventricular fibrillation, ventricular tachycardia, or atrioventricular block in cases hospitalized for SARS-COV2, was correlated with a remarkably enhanced death.[19] Higher levels of troponin have been associated with a risen occurrence of malignant ventricular arrhythmia, proposing that arrhythmia may be the outcome of other complications.[14] Moreover, subjects with advanced SARS-COV2 are usually treated with antiviral drugs and antibiotics that are known to cause arrhythmias in some subjects.[15,20]

Multisystem inflammatory syndrome in children (MIS-C): Several studies remarked that SARS-COV2 positive subjects had high blood markers indicative of inflammation such as C-reactive protein (CRP).[21] Furthermore, pediatrics with more severe presentations were observed to have

remarkably higher CRP levels than those with a milder appearance.[22] Beginning in late April 2020, a hyperinflammatory syndrome possibly associated with COVID-19 has been described in increasing numbers of pediatric.[23] Pediatric Multisystem Inflammatory Syndrome (PMIS) associated with COVID-19 shares many similarities with Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS), including multiple inflammatory markers and acute cardiac involvement.[10,24,25] Taking into the statement that in September 2021 there were 4.7 million cases of SARS-COV2 and that pediatrics account for 2%-5% of these subjects, the predicted incidence PMIS estimates for about 0.2%-0.6% of children COVID-19 diseases.[26] MIS-c is an established severe potentially fatal clinical demonstration of COVID-19 disease with different definitions. Centers for Disease Control (CDC) describes MIS-c in cases with SARS-COV2 infections and all four criteria: (1) Age under 21 years; (2) Verified COVID-19 disease or exposure during last 4 weeks; (3) Clinical manifestation with fever > 38°C for more than 24 hours, proof of significant inflammation in laboratory finding and critical multiorgan disease (4) Other examinations should be ruled out.[27]

Laboratory testing for MIS-C

Clinical presentation for diagnosis of MIS-C is fever >38°C for more than 24 hours. The proof of important inflammation of MIS-C in laboratory information includes increased CRP, erythrocyte sedimentation rate (ESR), IL6, d-dimer, fibrinogen, procalcitonin, ferritin and lactic acid dehydrogenase (LDH). Also, acute multiorgan disorder involves heart, lung, hematologic, neurologic system, skin, gastrointestinal or kidneys, requires to be hospitalized. Cardiac presentations of this syndrome are systolic dysfunction, aneurysm development in coronary arteries, and high cardiac biomarkers including cardiac troponin I (cTnI) and N terminal-pro brain natriuretic peptide (NT-pro BNP).[28] Although the state description is nonspecific and verifying laboratory examination does not exist. Consequently, it might be questioning to differentiate MIS-C from other situations with overlaying clinical demonstrations such as severe SARS-COV2 and Kawasaki disease (KD), making doubting to know the exact incidence of the disorder.[26]

Congenital Heart Disease during SARS-COV2 infection: Congenital heart disease (CHD) is one of the most commonly recognized congenital diseases troubling almost 0.8% to 1.2% of live births worldwide.[29,30] At the moment, there is no credible information with concerns to a load of infected infants with CHD and the SARS-COV2 associated morbidity and fatality in this context. Some studies are concentrating on pediatrics with CHD and SARS-COV2, essentially restricted to occasional case reports or small case series.[26] Patients with an underlying cardiovascular disorder are susceptible to more acute SARS-COV2 crisis and have a greater fatality.[20] It has been proposed that the milder demonstration of children patients with SARS-COV2 doesn't refer to the cases with CHD. Laboratory examinations of CRP and partial thromboplastin time (PTT) were higher in these cases.[31] These pediatric patients may be more likely to develop clinical deterioration if they suffer bilateral pneumonia or acute respiratory distress syndrome (ARDS), particularly those with uncorrected complex cardiovascular problems and reduced cardiopulmonary function. Aside from the hemodynamic load, some of these pediatrics might have related comorbidities including liver impairment, lung disease, neurological sequelae, renal failure, and impaired immunity correlated with probably attendant syndromes (DiGeorge syndrome, Down syndrome, heterotaxy syndrome with asplenia). Due to the documented myocardial crisis of SARSCoV-2 contamination in both adults and pediatric, and the heightened death seen in adult patients with pre-existing cardiovascular disorder and children CHD

with other viral infections (respiratory syncytial virus and Influenza), there is a probability that COVID-19 infection may induce new-onset of cardiac problems or a worsening of the basal situation in this sensitive population.[26]

Pathophysiology of Cardiac involvement in COVID-19

While the mechanism of cardiac damage is not entirely determined, there is information documenting SARS-COV2 and its impacts on the cardiovascular system.[7] Increased data propose that cardiac complication is common, especially in a case hospitalized with SARS-COV2 infection. Various mechanisms have been proposed for cardiac injury based on investigations on prior SARS-CoV and MERS-CoV epidemics and the currently continuing SARS-COV2.[32,33] SARS-COV2 may result in cardiac injury through the following multiple mechanisms.

Direct viral infection

COVID-19 viral attack of cardiomyocytes and direct injury by this way has not been well recognized in pathology investigations.[33] It has been established that COVID-19 infection has different types of cardiovascular manifestations in formerly healthy infected cases. The similarity between Corona virus spike protein (S protein) and ACE-2 receptor that is placed in cardiomyocytes, kidneys, intestines and the lung epithelial tissue may reveal some cardiac involvements of COVID-19 infection.[20] SARS-CoV2 utilizes its S-spike to bind ACE2 receptors as an entrance point to the cell. This receptor is expressed in both type1 and type 2 pneumocytes but too expressed in other kinds of cells, such as endothelial cells. ACE2 is an inverted regulator of the renin-angiotensin system(RAS).[34] This interaction of COVID-19 with ACE2 can result in alterations of ACE2 pathways causing acute damage to the lung, heart, and endothelial cells.[35,36] Moreover, ACE2 is expressed in the heart, and the COVID-19 virus applies this enzyme as a receptor for entrance into the cell. It is unclear at this time, nevertheless, if COVID-19 binding changes ACE2 expression or induces dysregulation of the renin-angiotensin-aldosterone system (RAAS) pathway.[7]

Deregulated immune response & cytokine storm

Systemic inflammatory response: SARS-COV2 may induce cardiac injury indirectly due to an upsetting immune-inflammatory response and cytokine storm.[37] As a part of the systemic inflammatory response of acute SARS-COV2 infection, a high level of cytokine wave, that can induce damage to various organs, such as cardiac myocytes, has been documented. Researches have revealed raised levels of proinflammatory cytokines in cases with critical SARS-COV2 infection. Cytokine storm such as an enhanced level of Interleukin 6 (IL-6) and tumor necrosis factor-a (TNF- a) and the systemic inflammatory response also direct myocardial damage is accountable for myocarditis and following ventricular dysfunction as a well-recognized problem in COVID-19 disease.[38,39]

CYTOKINE RELEASE SYNDROME (CRS)

Chemokines and Inflammatory cytokines including TNF-α, IL-6, interleukin-1b (IL-1b), and monocyte chemoattractant protein-1 (MCP-1) were remarkably raised in acute SARS-COV2 subjects.[40] The high cytokine levels may also lead to the deadly difficulties of SARS-COV2. In acute SARS-COV2 cases with raised inflammatory cytokines, autopsy pathology has shown tissue necrosis and interstitial infiltrations with macrophage and monocyte in the lung, heart, and gastrointestinal mucosa. The data of poor results of SARS cases treated with corticosteroids do not approve corticosteroid prescription for COVID-19.[41] The immunomodulators may be a helpful supplement to antiviral treatment. Among the extreme cytokines, IL-6 is one of the key cytokines. Extreme IL-6 signaling leads to various biological outcomes such as

enhancing cardiac arrhythmia, vessel permeability, and decreasing myocardium contractility.[42] It is a blockade targeting the host immune system that may be useful for SARS-COV2. The drug tocilizumab is a recombinant humanized monoclonal anti-IL-6 receptor antibody.[17]

Coagulation Abnormalities and Thrombosis

Thrombosis and COVID-19: Hypercoagulation conditions due to systemic inflammation, stability secondary to moderate to critical disease, lung endothelial injury also hypoxemia are suggested as the main mechanisms for pulmonary thromboembolism and thrombus formation in cardiac chambers.[43,44] Ischemic coronary damage after thrombus formation in coronary arterial bed in hypoxemic subjects is accountable for myocardial infarction and unbalanced coronary syndromes in the COVID period that can result in cardiac arrhythmia and ventricular dysfunction.[45] Myocardial ischemia, side effects of drugs, underlying myocarditis and, electrolytes abnormalities have been suggested as the fundamental mechanism for cardiac arrhythmias.[27]

Venous Thromboembolism: COVID-19 is related to coagulation irregularities, which can result in thromboembolic events.[46] Thrombotic events, which most usually happen in COVID-19, are mainly venous thromboembolism (VTE) and are correlated with enhanced illness severity and worse clinical outcomes. The heightened risk of VTE postures a significant difficulty to attending for 31% - 40% of critically sick COVID-19 patients.[47] Distinguishing microvascular irregularities in COVID-19 involve endothelial inflammation, disturbance of intercellular joints and microthrombi formation. A definite COVID-19-associated coagulopathy along with raised cytokines and activation of platelets, endothelium and complement happen in COVID-19, which is more common with worsening illness severity.[48] Disseminated intravascular coagulation (DIC) happened in 71.4% of subjects who died of acute SARS-COV2. The DIC cases had high venous thromboembolism degrees, raised D-dimer levels, raised fibrinogen levels, lowering antithrombin levels, and pulmonary obstruction with microvascular thrombosis and obstruction. Fibrin displacement in the pulmonary microvasculature committed to ARDS in cases with concurrent determinations of DIC.[49,17]

Myocardial Damage due to Severe Hypoxia: Severe hypoxia from serious respiratory injury made by the virus may lead to oxidative stress and myocardial damage from enhanced myocardial oxygen requirement in the appearance of severe hypoxia because of ARDS.[7] Myocardial oxygen supply/request mismatch; As an outcome of enhanced cardiometabolic requirement correlated with the systemic infection and continuous hypoxia induced by acute pneumonia or severe respiratory distress syndrome can occur to enhanced request in the front of short supply beginning to myocardial injury.[35]

Discussion

Former studies around the pneumonia outbreak induced via COVID-19 were principally based on data from adult groups. Restricted information is available for pediatric with SARS-COV2, particularly for infected infants. The main reason for death due to COVID-19 disease has been reported and pre-existing comorbidities remarkably enhance the disease death.[50] Nonetheless SARS-COV2 infection in pediatric is less frequent and with milder manifestations than when happening in adult cases, it is not without the risk of cardiac complication, notably in the cases with a history of CHD.[9] Children less than one year old are at the highest risk for hospitalization and severe disease. Mortality due to COVID-19 has only been published in a few children from different countries.[51] lungs are not the only SARS-COV2 target but also the cardiovascular system may be affected.[9] Few

of the studies reported pediatric with CHD and SARS-COV2, and so the effect of the virus on this special patient group is not cleared. Nonetheless, pediatric seem less susceptible to SARS-COV2 than adults overall.[7] Given the raised heights of cytokine levels seen in cases with acute SARS-COV2 disease, as well as the note that some cases with SARS-COV2 decline quickly with cardiogenic shock and multi-organ failure, more investigations should be done to examine COVID-19 and its potential role in fulminant myocarditis.[7] Generally, the broad spectrum of presentations including subclinical myocardial injury, myocarditis, cardiac arrhythmias, stress cardiomyopathies, pulmonary thromboembolism, and thrombus formation in cardiac chambers and the vascular bed has been described in SARS-COV2 infection. It seems COVID-19 can affect different parts of the heart; however, the myocardium is more engaged. There is yet scarce information about the role of cardiovascular complication in SARS-COV2 in infants. The basic pathophysiology of SARS-COV2- related cardiovascular difficulties is not entirely realized, However In our review, we explain several mechanisms include direct viral infection, Systemic inflammatory response, Coagulation abnormalities and thrombosis, and hypoxia, that have been proposed as possible mechanisms of Cardiac complications. Myocardial damage is a significant prognostic factor in SARS-COV2 and is strongly related to fatality. Severe cardiac damage characterized by raised high sensitivity troponin levels is usually seen in severe cases. Myocarditis is now determined as a risk factor for increased death in patients with COVID-19. Severe heart failure due to multi system inflammatory syndrome in pediatric is a recognized presentation of COVID-19 disease in pediatric subjects.[52] Cases with SARS-COV2 usually have raised levels of D-dimer, moderately lowered platelet counts and lightly prolonged prothrombin time. Furthermore, levels of factor VIII and fibrinogen were increased in these patients, showing a hypercoagulable state.[53,20] It is proposed that fundamental cardiovascular disorder drives increased morbidity and fatality in cases with SARS-COV2 infection.[54] CHDs are the most frequent form of congenital disorder and have a broad spectrum from asymptomatic mild models of the valvular lesion and trivial shunts to acute complicated faults that contradict with the duration of life.[27] As reported by the available information, children subjects with CHD may be more susceptible to more acute SARS-COV2 disease with enhanced death.[27] Besides, medicines presently used to treat SARS-COV2 may also affect the cardiovascular system.[12] It is advised to request cardiac-specific examinations such as NT-pro BNP and cardiac troponin to assess plausible injury of the heart. This seems infants must be monitored more exactly, particularly those with basic cardiovascular co-morbidities. It was recognized that these cases were more probably to need hospitalization, admission to NICU, and had lower mortality results.

Conclusion

The mechanisms of Pathogenesis of cardiovascular indications in adults and infants are similar but CHD and MIS-c in infants are more important. In neonates and pediatric, prior cardiac operation is correlated to the risk of a more acute form of the disease, being admitted to the intensive care unit, and requiring intubation to mechanical ventilation. The existence of cardiovascular presentations may also affect the intensity of SARS-COV2, and basic cardiovascular diseases may raise fatality. So infants must be monitored more carefully, and it is recommended to request cardiac-specific examinations such as NT-pro BNP and cTnI to evaluate possible injury of the heart.

Conflict of Interests

Authors have no conflict of interests.

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