

CARDIOVASCULAR MANIFESTATIONS OF SARS-CoV-2 IN CHILDREN – A REVIEW

Cardiology

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ABSTRACT

Initially COVID 19 infection with its associated complications was mainly reported in adult population. With increase in the number of cases as well as duration of the pandemic many children started presenting with atypical illnesses. Here we aimed to summarise the mechanism, clinical findings, investigations and management of COVID 19 related cardiac illness in the children. A multidisciplinary team including paediatricians, cardiologists, critical care specialists and infectious disease specialists should be involved in the management of COVID-19 affected children.

KEYWORDS

INTRODUCTION:

After the COVID 19 outbreak most of the data and case series were identified in symptomatic adult individuals across various parts of countries. During the early phase of COVID 19 pandemic, initial reports suggested that children were relatively spared and they suffer from mild or no symptoms, less frequent hospitalisations and death rates [1]. However after few months of the beginning of pandemic wide variety of clinical manifestations were observed in the pediatric population such as myocarditis, heart failure and unusual febrile illnesses that have features of Kawasaki's disease, toxic shock syndrome, acute abdominal conditions, and encephalopathy, along with other reports of children with fever, elevated inflammatory markers, and multisystem involvement [2,3]. Here our aim is to summarise the previous outbreaks caused by corona viruses and the cardiac manifestations of COVID 19 and its pathogenesis in children.

LESSONS LEARNT FROM THE PAST:

The corona viruses are single stranded RNA viruses with the capacity of rapid mutation and combination. At present COVID 19 pandemic is still evolving and we are in need to understand the previous outbreaks of viruses belonging to corona viruses family for the better

management of pandemic. As of now seven different strains were identified, it includes HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, which generally cause self-resolving infection. Others include Severe Acute Respiratory Syndrome Corona virus (SARS-CoV), Middle East Respiratory Syndrome Corona virus (MERS-CoV) and SARS -CoV2 which causes lethal pneumonia and hospitalisations [4][5].

The endemic corona viruses cause mild upper respiratory infections, which is usually self limiting accounts for 15 to 30%. The endemic corona viruses can be isolated from 4 to 6 % of children in nosocomial settings and 8% in ambulatory settings. Children under the age of 3 years and those with underlying cardiac illness are mostly affected [6]. El-Sahly et al concluded that those infected with common cold viruses underlying cardio pulmonary diseases were present in 35% of individuals aged < 5 years, in 93% aged between 5 and 35 years, and in 73% aged >35 years [7]. Falsey et al concluded that corona viruses typically cause common colds in young adults and may lead to hospitalization in frail elderly persons with underlying heart and lung problems [8].

The SARS-CoV, belonging to beta corona group uses ACE2 receptor to enter host cell in the respiratory epithelium, arterial smooth muscles, epithelial lining of small intestine and immune cells [9][10]. In contrast to adults there are 3 case series that report a total of 41 children who were affected by SARS-CoV. The disease was mild or asymptomatic or they recovered quickly from the infection and no death was reported in those children [11][12]. In adults Peiris et al reported 75 patients admitted with SARS-CoV acute myocardial infarction was the cause of death in 2 of 5 fatal cases [13]. Li SS et al conducted a prospective study with 46 adult patients with SARS-CoV infection at 30 days follow up in which systolic function recovered completely and minor diastolic abnormalities were seen [14]. Yu CM et al concluded that in 121 patients admitted with SARS-CoV in adults, 12 patients had underlying cardiovascular disease and tachycardia was the most common finding followed by hypotension [15].

The MERS CoV belonging to beta corona viruses uses a serine peptidase, dipeptidyl peptidase 4 as the receptor to enter the host cell. Most case series reported that only a very few (0.1% -4%) of children were affected. During 2012-13 epidemic, the children presenting with upper respiratory infections were tested for MERS-CoV in Saudi Arabia none of them found to be positive [16]. There are two small case series, one in 31 children and the other in 7 children. In the case series conducted on 7 children, most common symptoms was fever (54%), vomiting and diarrhea (28%), cough and breathlessness (14%), and two of them required oxygen supplementation. In the case series involving 31 children two of them were died. In both studies 42% were asymptomatic [17]. In adults Badawi et al reported that a systematic analysis of 637 MERS-CoV patients showed that 30% of cases had underlying cardiac diseases, 50% had hypertension, 50% had diabetes, and 16% had obesity [18].

SARS-COV 2 AND CHILDREN:

COVID 19 seems to be less aggressive in children when this disease is compared to adults. The most common symptoms include fever, cough, rhinorrhea and sore throat. Some pediatric patients presented with gastro intestinal symptoms like vomiting and diarrhea as well. It is proposed that the initial phase of this pandemic causes severe lung involvement in children in only 2-6 % cases requiring frequent hospitalisations [19]. In contrast to children the 80 – 85 % of adult individuals the symptoms include loss of smell and taste, sneezing, cough, fever, and shortness of breath and 10-15 % of adults are presenting with severe pneumonia and acute respiratory distress syndrome [20]. In a study published from China on adults shows that cardiac involvement was around 12%, and other study from the same country shows arrhythmias and myocardial injury were reported in 16.7% and 7.2% of them [21]. The data relating to the COVID 19 in paediatric age group is relatively sparse and very few cases were reported and in those reports cardiac involvement also described.

CARDIO VASCULAR SYSTEM IN CHILDREN WITH COVID 19:

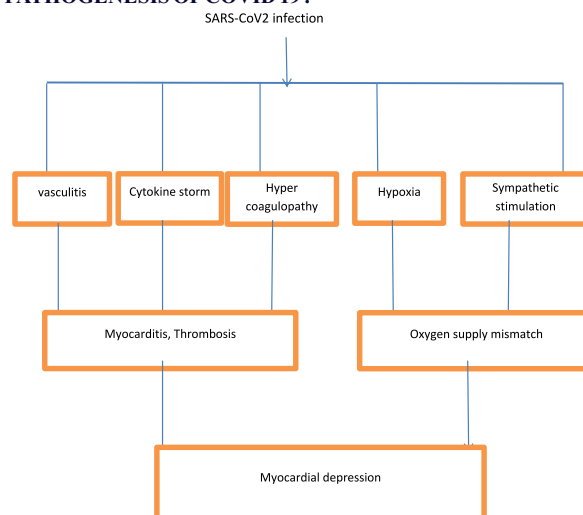
It has been proved that adults with more comorbidities leads to worse prognosis in COVID 19 patients, similarly, children with comorbidities like congenital heart diseases also have poor outcomes [22]. A past medical history of broncho pulmonary dysplasia, corrected congenital heart surgeries, hemoglobinopathies, immune deficiency syndromes and malnutrition are predisposing factors for COVID 19 infections [23].

The involvement of cardiovascular system in those children affected by COVID 19 can be classified accordingly into asymptomatic and symptomatic. The majority of children are asymptomatic but they might be the responsible for community transmission. Some of the children are symptomatic and those who are symptomatic are classified into two categories depending on the mechanism of cardiac injury.

DIRECT INVOLVEMENT: The data related to COVID-19 and its pediatric involvement is relatively sparse and very few severe cases were reported. In those cardiovascular system also involved in some of them, thus showing heart may be possible target in pediatric age as well. Cui et al reported a case report presenting a 55 day old infant multiple organ damage including heart damage, on day 4 the cardiac enzymes and troponin levels were raised and after 7th day the general condition of the patient improved and 3 days later troponin levels became normal [24]. Sun et al conducted a retrospective analysis of small case series of 8 children, who admitted in critical care, a 13

month old baby developed cardiac failure, coagulopathy and multiple organ damage [25]. Xia et al concluded that the rise in procalcitonin is common in pediatric population in contrast to adults and it shows that out of 20 patients enrolled, 7 of them had previous congenital or acquired cardiac pathology, in particular two of them survived [26]. Similar to adults, the children with comorbid conditions have worse clinical prognosis. Zheng et al conducted a retrospective analysis of 25 children the most aggressive COVID 19 infection were seen in two babies those who were operated for previous congenital heart disease [27]. Direct cardiac involvement occurs in the form of acute myocarditis, hypoxia induced metabolic acidosis causing cardiac depression, rhythm disturbances causing life threatening arrhythmias, drug induced QT prolongations, cytokine storm caused by the increased levels of inflammatory molecules IL-1 β , IFN- γ , IP-10, MCP-1, and lymphocyte Th1 activation. A rise in troponin I levels is seen in adults, those who were admitted in intensive care units as well as in severe lung involvement patients. However in pediatric age group troponin levels are not well defined. Some data have been gathered supporting rise of troponin levels as a marker of myocardial injury in this group as well [28]. The severe pneumonia leads to hypoxia and pulmonary hypertension leading to right ventricular disease further compromising cardiac output [29]. The intubated critically ill-pediatric group shows adverse cardiovascular outcomes by decreased venous return, right ventricular dysfunction and reduced left side distensibility [30]. The increased sympathetic stimulation may also leads to increased arrhythmic events.

PATHOGENESIS OF COVID 19 :



POST INFECTIOUS (Indirect): Several Countries reported atypical presentation of pediatric cases with hyper inflammatory processes and shock associated with COVID 19 [31]. This syndrome presented with unusual febrile illness like that has features of Kawasaki's disease, toxic shock syndrome, Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome.

A case definition for this emerging disorder was published in late April 2020, termed "pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)," or PIMS-TS [32]. On May 13, 2020, the New York State Department of Health (NYSDOH) released an interim case definition, and on May 14, 2020, the Centers for Disease Control and Prevention (CDC) released a Health Alert Network advisory about multisystem inflammatory syndrome in children (MIS-C) associated with Covid-19 [33].

The most common clinical presentations of MIS-C includes persistent fever, asthenia, diffuse erythematous polymorphic rash, non-purulent conjunctivitis, and prominent gastrointestinal symptoms. The clinical features resembled Kawasaki disease like mucosal changes, rash, peripheral edema, and conjunctivitis. In contrast with adults, odynophagia and lower respiratory symptoms were less common [34]. In severe cases because of dysregulated immune response some developed hypotension and shock which requires icu care, inotropic support and ventilatory support. Children with overweight may predispose to MIS-C, and most of the patients reported were healthy not associated with any pre-existing congenital heart disease or

immune deficiency diseases. Most of the case series shows that the African as well as Hispanic subjects may have significant predisposing factor for MIS-C [35][36]. These ethnic groups are associated with higher vitamin D levels, their lungs mature earlier, and they are genetically predisposed to hyper inflammation causing MIS-C [37].

The majority of children have serologic evidence of prior infections or family history of exposure and they found to have higher percentage (75-100%) of IgG antibodies. Minority of patients have RT-PCR positive for SARS-CoV2. Some reports suggested it varies around 20-53%. It clearly shows the evidence of post infectious dys regulated immunological response to SARS-COV2.

The pathogenesis of MIS-C involves the following phases;

1. Phase 1-Early infection
2. Phase 2-pulmonary phase
3. Phase 3-immunological phase

Typically the early infection phase 1 is mildly symptomatic or asymptomatic in children. Following this phase the children affected with SARS-CoV2 develops an immune dysregulation, but in adults it is found to be severe by causing direct alveolar injury. The pulmonary phase-2 is less severe or no lung involvement in children. The another reason was postulated that children have less number of ACER2 receptors which was the primary target involving in the pathogenesis of SARS-CoV2 infections. The immune dysregulation is caused by macrophage activation which activates t helper cells producing pro inflammatory cytokines such as IL-6, IL-12, TNF-beta, IL4 leading to cytokine storm further activating neutrophils, monocytes and B-cells producing antibodies. (Phase 3-immunological phase). Thus the post infectious inflammatory phenomenon plays a major role in developing MIS-C.

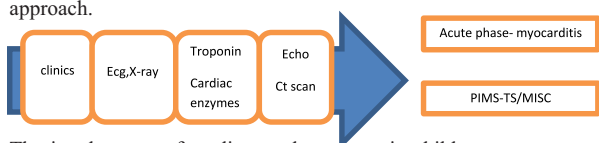
Both the initial case reports and subsequent studies show that left ventricular dysfunction is seen in 35 -100 % of children. The first case series published in UK, Riphagen et al concluded that LV dysfunction was present in 75%(6/80) of children. Belhadj et al. reported a selected cohort of 35 MIS-C patients who developed acute LV failure (LV ejection fraction (LVEF) < 50%) or shock, fever, and elevated inflammatory markers. None of them died and they successfully recovered [38].

Coronary artery involvement leading to dilations or aneurysms is frequently seen in 6-24 % of MIS-C patients. In acute phase, the hyper inflammatory processes and fever leading to coronary artery dilatation. Some case reports has shown that giant coronary aneurysms are occurring due to intimal disruption. The follow up of MIS-C patients is important in detecting aneurysms after discharge.

The arrhythmic manifestations were also detected in MIS-C patients in 7-60% of patients. The most frequent manifestations are non specific, ST segment changes, QT prolongation, atrial or ventricular premature beats. First degree or second degree heart blocks were also reported in one series, atrial fibrillation were also seen in two series.

CLINICAL APPROACH TO CHILDREN WITH CARDIAC INVOLVEMENT:

Given the lack of definitive treatment, more contagious, high cost and limited drug resources the management is not recommended for prevention or non hospitalised patients. A multidisciplinary team including paediatricians, cardiologists, critical care specialists and infectious disease specialists should be involved in the management of COVID-19 affected children. Figure 2 shows the proposed clinical approach.



The involvement of cardiovascular system in children may present with shock requiring adequate fluid resuscitation. The paediatric resuscitation guidelines should be followed. Adequate inotropic and ventilator support should be provided. Since it is well established that the pathogenesis of MIS-C and infective myocarditis caused by cytokines, there may be some benefit of using immunomodulator therapy in these patients [39]. Slower IV Immunoglobulins may be considered for those patients with significant myocardial involvement. The use of biologic drugs (tocilizumab, anakinra, infliximab) could be

considered in patients with severe or critical illness, especially if they do not respond to first-line treatments. The anticoagulation and or antithrombotic measures should be considered in the children with myocardial involvement, coronary artery dilations, documented thrombogenic event, arrhythmia and abnormal coagulation profile (D-Dimer >3 mg/ml). The antivirals (remdesivir) is particularly useful in RT-PCR positive and active COVID 19 subjects but doesn't have much role in MIS-C [40]. It is very essential that the recovered children should be in adequate follow up for atleast six months in the out patient department. Most of the MIS-C patients will recover before discharge and some patients with myocardial dysfunction, coronary artery dilatation should be in follow up. The exercise limitation and restricted physical activity for atleast 6 months should be advised [41]. Based on experts opinion the preparticipation ECG, Echocardiogram and if needed exercise testing should be prescribed for children participating in competitive sports.

CONCLUSION:

Most studies published about COVID-19 are mostly based on adult population from China. Data on children is limited and clinical manifestation is diverse, hence, there is a need of more study and data in pediatric group. Since the management and clinical follow up of both direct and post infectious manifestations are different, the knowledge of MIS-C is important. Proper MIS-C registry should be maintained all over world for the immunisation against SARS-CoV 2 infections. Although COVID 19 causes less severe infections in children than adults, it is not always without the risk of cardiac involvement. Further studies are needed for in depth understanding of COVID 19 infection in the pediatric age group.

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