Prevalence of Cardiac Dysfunction in MIS-C in Children (MIS-C) related to COVID-19

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Abstract

Background: COVID-19 in children normally causes mild infectious illness, but serious repercussions can occur in combination with both acute infection and related phenomena in children, like the Multisystem Inflammatory Syndrome (MIS-C). In rural hospitals, there is less information available on Cardiac abnormality in MIS-C. **Objectives:** To know the prevalence of cardiac dysfunction of MIS-C children having COVID-19. Methodology: The MIS-C patients in this prospective research will be diagnosed using WHO criteria. On admission, MIS-C patients with cardiac marker positive will have an anomaly in one or more of the following: Electrocardiography, Brain Natriuretic Peptide (BNP), serum troponin, and/or echocardiogram. **Results:** We will determine the prevalence of cardiac dysfunction in MIS-C when the study is completed. We will compare outcome factors such as hospital stay days, ICU admission, and death based on the therapy received. We all also study the correlation between the inflammatory marker and LV dysfunction. **Conclusion:** The study will most likely provide information on the prevalence of heart abnormality in MIS-C children. Also, the outcome of the MIS-C with cardiac dysfunction will be revealed.

Keywords

Cardiac dysfunction; MIS-C; COVID-19; Children; Coronary dilatation

Introduction

In December 2019 in Wuhan, China a new strain of coronavirus found which is known as novel coronavirus which involves mainly respiratory tract system.

According to genome analysis, they found that it is beta coronavirus and it is connected to SARS virus. While the majority of COVID-19 patients have mild to moderate sickness, nearly 14% have a severe condition that needs inpatient treatment and oxygen assistance, and 5% require admission to an intensive care unit.[1]

Because of infection and septic shock, MODS, ARDS and cardiac damage COVID-19 may be exacerbated. [2] Children with COVID-19 typically have mild symptoms than adults, with cough and fever is most common, and co infection has been discovered. [3,4]

Only a few cases of newborns with COVID-19 have been documented; those who did develop mild illnesses. [5] There is no major difference in COVID-19 symptoms in non-pregnant or pregnant and in adults. Droplet precautions help to prevent the spread of respiratory infections caused by large droplets. Wear a medical mask if you are operating within one meter of the patient.

COVID-19 typically causes a milder pathogenic illness course in children, but serious complications can occur in interaction with both acute infection and related phenomena such as MIS-C. Adults have been developing neurological symptoms ranging from a simple headache to seizures, peripheral neuropathy, stroke, demyelinating diseases, and encephalopathy.

Neurological problems show widely depending on age and underlying comorbidities, as do respiratory and cardiac signs of COVID-19. Cardiovascular abnormalities have been observed in people suffering from this condition, in addition to pulmonary complications and limitations associated with infection.

Clinical outcomes have included myocardial infarction, valvular abnormalities, myocarditis, increased coagulopathies which cause peripheral vascular problems, and even left ventricular dysfunction which leads to heart failure. Heart cell damage caused by direct invasion by virus or by

indirect method like increased inflammatory marker and coagulopathy or metabolic abnormalities are the most likely mechanisms underlying cardiac damage. [6,7] In rural hospitals, there is less information available on Cardiac Dysfunction in MIS-C.

Research Question

What is the prevalence of Cardiac Dysfunction in Children with COVID-19-Induced MIS-C (MIS-C)?

Aim and Objectives

Aim: To identify the prevalence of cardiac dysfunction in MIS-C related to COVID-19.

Objective:

1. To illustrate the demographic characteristics of MISC related to COVID-19

2. To study the correlation of the inflammatory marker and LV dysfunction

3. To study the outcome of the MIS-C with cardiac dysfunction

Material and Methods

Setting: The Jawaharlal Nehru Medical College, DMIMS, Sawangi Meghe, Wardha is a rural medical college located in Maharashtra.

Study Design: Prospective observational cohort study

Study population: Diagnose case of MIS-C

Time Frame / Duration: 12 months

Methodology

On admission, all children with symptoms RTPCR will be sent. Positive results are RTPCR positive in ICMR certified laboratory or antibody positive for COVID-19 in certified ICMR laboratory. In antibody IgG and IgM level will be detected and determine whether it is positive or not. After the caretaker's written informed agreement, the MIS-C study case will be enrolled in the research.

MIS-C definition: History of fever for ≥ 3 days in children of age between 0-19 years. And it should also have 2 out of 5 below features

1. Child may have rash/non-purulent conjunctivitis/muco-cutaneous inflammation.

2. Children may present with hypotension or septic shock.

3. Clinical features which suggestive of myocardial dysfunction, abnormalities in coronal vesse, and valular involvement and also include positive echocardiography finding or raised Troponin/NT- proBNP.

4. Raised coagulation profile.

5. Clinical features of acute intestinal problem like diarrhoea, vomiting, or pain in abdomen. And Child should have increased inflammatory marker like ESR,CRP OR procalcitonin. And there should be no other microbial cause which can leads to inflammation. And Children should have positive report of rapid antigen, covid antibody/covid RTPCR positive or there should be contact history. [8]

Method of Collection of Data

History

Parents will be inquired about the following history

1. Demographic characteristics: Child's name, sex, address, and religion.

2. Subject's conditions at birth: gestational age, birth weight

3. Detailed clinical history of the study case

Physical examination

1. Vital signs (tachycardia, tachypnoea, and hypotension) will be categorized based on age-appropriate norms. [9]

2. General physical examination and systemic examination will be done

Anthropometry

An anthropometric assessment will be performed. Anthropometric indices will be recorded as suggested of weight close to 0.1 kg by weighing scale machine and height close to 0.5 cm by Infantometer and stadiometer.

Following investigations will be done in the study subjects

i. Blood Test: Data on several laboratory indicators will be obtained, and high levels will be identified in comparison to age-appropriate values. [10-11]

1. Lactate dehydrogenase (LDH)

2. CBC with peripheral smera

3. ESR

4. CRP

5. Coagulation profile

6. Electrolytes- sodium,calcium,potassium

7. Serum Ferritin

8. Troponin/ CK or CK-MB

9. Fibrinogen

10. LFT, KFT

11. D-dimer

12. Procalcitonin (PCT) can increase significantly in systemic bacterial infections and sepsis.

13. Interleukin-6 (IL-6)

ii. Chest X-ray (CXR)

1.	The cardiothoracic ratio will be assessed in the standard way

2.	Assess for the consolidation

iii. CT chest/ HRCT: In children, CT chest will show ground-glass appearance and opacity in lower lobe and peripheral predominate, which resolved spontaneously

iv. Electrocardiograms (ECG): All individuals' 12-lead surface electrocardiograms will be acquired using single-channel electrocardiography equipment. The QRS interval, QTc dispersion (QTcd), and QT dispersion (QTd), HR, RR interval, RR variability, corrected QT (QTc), QRS axis, and QT interval were all recorded and were determined from all electrocardiograms.

v. Echocardiographic (ECHO)

● A transthoracic echocardiographic examination will be performed utilizing a Phillip Echocardiography machine equipped with phased array transducers operating at an 8 MHz frequency. M-mode echo is a common method for assessing LV function. As a result, pulsed and continuous wave Doppler, M-mode, 2-dimensional echocardiography, and color flow mapping will be done in every MIS-C case, utilizing standard views.

● Assessment of LV function

1.	LV dimensions: M-mode echocardiography used to determine this. All tracings will be recorded with cutting-edge technology.

2.	The 5/6 area length technique will be using to observe the systolic function of the left ventricle (LV), and LV dysfunction was described as LV ejection fraction (LVEF) of less than 50%. E/A wave ratios of mitral valve inflow Interrogation of Doppler and tissue Doppler imaging will be used to assess LV diastolic function. [12] The American Heart Association statement from 2017 described the classification of coronary artery dilatation, size of aneurysm and Kawasaki disease. [13] MIS-C in children who have a positive cardiac marker on admission will have an abnormality in one or more cardiac markers: serum troponin, brain natriuretic peptide, electrocardiogram, and/or echocardiography.

Outcome: Hospital stays days, ICU admission, and death will be the outcome variables [Figure 1].

Statistical Analysis

The data will be analyzed using the STATA program, version 10 for Windows. Descriptive statistics (frequency, mean, percentage, and standard deviation) will be used primarily to describe and characterize the data to make it more comprehensible. When applicable, Chi-square will be utilized for analytical statistics, and the correlation coefficient will be utilized to define the strength and direction of the relationship between two variables. ANOVA analysis and we will use student t-test to compare the three groups with different levels of illness severity, also in children who survived or non survived, in normally distributed and homogeneous data. Otherwise, the Kruskal-Wallis and Mann-Whitney-Wilcoxon tests will be employed as appropriate.

Expected Results

We will determine the prevalence of cardiac dysfunction in MIS-C when the trial is finished. We will compare outcome factors such as hospital stay days, ICU admission, and death based on the therapy received. We will also analyze the cardiac function depending on the treatment received. We all also study the correlation between the inflammatory marker and LV dysfunction. Finally, we will come to know the outcome of the MIS-C with cardiac dysfunction.

Discussion

COVID-19 occurs due to SARS-CoV-2, this is similar to bat SARS-related coronaviruses. [14-16] The common symptoms of the infection by COVID-19 are fever, cough, fatigue, sore throat, headache, myalgia, rapid breathing, vomiting, diarrhea, or abdominal pain. [17,18] The study was done by yasuhara J et al. [19] discovered that mild symptoms such as febrile illness (64%), rhinorrhea (16%), cough (35%), and no symptoms (15%) were the most common clinical signs in COVID-19 children. The presence of ground-like opacities was a typical radiological observation (54%). The most prevalent laboratory findings were decreased lymphocyte (33%), elevated C-reactive protein (40%), and D-dimer (52%). They discovered 17 individuals (15%) with the MIS-C in children, who described symptoms comparable to but different from Kawasaki disease, such as left ventricular dysfunction, shock, intestinal symptoms, and highly elevated inflammatory markers. Because of hypotension, 12% of the patients, along with 65% of MIS-C cases, required critical care. There was zero mortality. Finally, they discovered that COVID-19 children are frequently milder or asymptomatic. Infants, on the other hand, may become severely symptomatic and older children may go into severe MIS-C. Early detection of covid-19 who don't have any symptoms or have mild symptoms and MIS-C patient is important as by identifying these children will help in the prevention of transmission of the virus. Another study done by Alkan G et al. [20] did a retrospective study of MIS-C. MIS-C patients were divided into 3 groups (1.mild 2.moderate and 3.severe) and 3 age groups (five years, 5-10 years, and > ten years). They investigated 36 children who had MIS-C. (median age of 7.8 years and 52.8 percent male). In all age categories, the most common symptom (69.4%) was a clinical features coinciding with Kawasaki disease (KD). Most of parents brought children with complaint of feverish (100%), skin/mouth rash (69.4%), and intestinal problems (66.6%). The abnormality in echocardiographic abnormalities between the KD-like disease and the other clinical disease was not statistically significant (p > 0.05). All abnormal rhythm abnormalities were discovered in severe instances. Among the MIS-C patient, there were no fatalities. Finally, they reported that electrocardiographic and echocardiographic examinations are crucial in detecting MIS-C in children. Moreover, Pro-BNP can be used in the emergency room as a

screening process to detect children with persistent and unusual fever. During the COVID-19disease outbreak in France and Switzerland, Belhadjer Z et al. [21] collected clinical, biochemical, curative, and early data from children admitted to ICU in fourteen centers for cardiac shock, myocardial abnormality, and severe inflammatory state over 2 months. They enrolled the study's thirty-five children. The median age was 10 years (2-16 years). Comorbidities, such as asthma and obesity, were present in 28% of the participants. Gastrointestinal problems predominated. LVEF was less than 30% in one-third of the patient, inotropic treatment was necessary for 80 percent, and extracorporeal membrane oxygenation was being used in 28 %. The presence activation of macrophage (median D-dimer, 5284 ng/mL) and cytokine storm (median interleukin-6, 135 pg/mL) were markers of inflammation. The BNP level was raised (5743 pg/mL). 31(88%) of 35 patients was covid 19 positive. All children were given IVIG (intravenous immunoglobulin) and one-third were also given steroid therapy. In 25 of the 35 study participants who were released from intensive care, left ventricular function was restored. There was no mortality and all children who received extracorporeal membrane oxygenation were successfully removed from ECMO. They discovered that infants may suffer from severe cardiac decompensation as a consequence of an inflammatory state caused by COVID-19 infection (MIS-C in children). IVIG was found to be correlated with enhanced left ventricular function. The study conducted by Diorio C et al. [22] included admitted COVID-19 patients and classified them as either COVID-19 or MIS-C. COVID-19 individuals grouped as mild or severe disease. Cytokine levels, viral load, blood tests, and C5b-9 levels are obtained from the study. He listed 20 children in which (9 severe COVID-19, 5 mild COVID-19, and 6 are having MIS-C). TNF-α, IL-8, IL-10, IL-6, IL-8, and IFN-γ levels all were tested in the research. The study subject with MIS-C was differentiated from others with severe COVID-19 symptoms by TNF-α and IL-10. Individuals with severe COVID-19 diseases and MIS-C differentiated by the presence of burr cells on peripheral smear images and Cts. Children exposed to COVID-19 are in danger of experiencing severe COVID-19 and MIS-C, according to the author. By cytokine analysis and peripheral blood screening tests MIS-C patient and severe COVID-19 patient may benefit. From April 23 to May 23, 2020, Kaushik S et al. [23] performed a prospective study in pediatric critical care settings in New York City. Demographic and clinical data were taken. They found 61% were male, 45% Hispanic/Latino, and 39% black, 33 cases with MIS-C, with a median age of 10 years. Complications were found in 45% of the patients. The most of children (93%) were have fever and vomiting (69%). 63% of patients had a decreased LVEF with a median EF of 46.6 % (IQR, 39.5-52.8). pro-B-type natriuretic peptide, CRP, procalcitonin, d-dimer, and were all raised in all individuals. IVIG being used in 18 patients (54%), mechanical ventilation in 5 cases (15%), corticosteroids in 17 cases (51%), ECMO was used in 1 case (3%), and intra-aortic balloon pump in 1 case (3%), vasopressors in 17 cases (51%), tocilizumab in 12

cases (36%), remdesivir in 7 cases (21%). The LVEF improved in 95% of individuals who had a poor EF. After a median stay inside the pediatric critical care unit of 4.7 days (IQR, 4-8 days) and a stay in hospital of 7.8 days, all children got discharged (IQR, 6.0-10.1 days). One patient died during ECMO due to a stroke. They find that critically ill children with COVID-19 associated with MIS-C have a broader severity spectrum than previously reported but require careful supportive ICU care. almost all patients healed fully. Another observational study was conducted by Jain S et al [24] at 4 tertiary institutions in Mumbai. In Mumbai, they found 23 children (11 boys) with the MIS-C with COVID-19 with a median of 7.2 (0.8-14) years. RT-PCR or antibody positivity was observed in 39.1% and 30.4% of the patients, respectively; 34.8 % of the cases had a positive contact. When compared to patients who did not come in shock, 65% were older (P=0.05) and had a significantly higher chance of myocarditis with raised BNP, troponin, and LV dysfunction, as well as increased neutrophil and lymphopenia. In all, 26% of patients exhibited coronary artery dilatation. Steroids were the most often used treatment (96%), usually in combination with intravenous IVIg (65%). The prognosis was good since there was just one death. More study and longer-term follow-up of MIS-C patients are needed to improve our surveillance criteria, therapeutic, and diagnostic. Shobhavat L et al [25] did a cohort study on MIS-C in children infected with the COVID-19. They showed 21 cases, 11 of them were females, with a median of 7 years [interquartile range (IQR) 1.9-12.1]. A positive COVID-19 resulted in 8/21 cases, while a positive antibody test resulted in 16/21 cases. All patients had a fever, with gastrointestinal symptoms second place (16/21). One of the children had aplastic anemia, and the others were healthy. Almost all (n = 20/21) of the patients came with a shock, and 90% required vasoactive medication, with a median Inotropic Score of 40. (IQR 20-95). 13 of the youngsters needed mechanical ventilation, and one requires peritoneal dialysis. 9 children had LV failure on echocardiography, and 5 had coronary artery dilatation. serum IL-6 levels [215 ng/L (IQR 43-527)], CRPV98 mg/dL (IQR 89-119)], S. ferritin [710 mg/dL (IQR 422-1,609), were persistently elevated as inflammatory markers. 18 Pulsed methylprednisolone, eleven IVIG, and four tocilizumab were administered to cases. 18 children (86%) were discharged from the hospital, while 3 children not survived due to complications. Finally, they discovered MIS-C in previously healthy toddlers who experienced fever, intestinal problems, and shock. Early shock management was used, as well as immune modification using intravenous immunoglobulin and methyl-prednisolone.

Conclusion

The study will most likely provide information on the prevalence of heart dysfunction in MIS-C patients. We will also learn the result of the MIS-C with cardiac dysfunction.

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