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MORBIDITY AND MORTALITY PROFILE OF CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH COVID 19 INFECTION: A TERTIARY HEALTH CENTRE STUDY IN SOUTHERN RAJASTHAN

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ABSTRACT **Objective: -** To study the Clinical Characterstics, Laboratory Parameters and Treatment outcome of Children of age < 18 years having Multisystem Infammatory Syndrome of Children (MIS-C) associated with Covid 19 infection, admitted at Bal Chikitsalay , RNT Medical College, Udaipur Rajasthan.

Method: - A Hospital based prospective study conducted at Tertiary centre on children <18 years , admitted from April 2021 to July 2021 with Multisystem involvement associated with Covid 19 infection and fulfilling the criteria proposed by Centre of Disease Control and Prevention . Children who had alternate diagnosis and not consenting for study were excluded.

Results:-23 Childern were enrolled in this study, 12 were Males and 11 Females. Fever (100%) was present in all as it is a mandatory criterion, Gastrointestinal symptoms (95.6%) and Mucocutaneous Rash (56.5%)were also present. On examination 16 children (69.5%) had Hypotension followed by Respiratory (34.7%), Cardiovascular (21.7%) and Neurological were involved in 8.6% patients. Laboratory profile consisted of raised C reactive protein (82.6%), raised D –DIMER (52.1%), incresed Neutrophil: Lymphocyte ratio (34.7%), and increased Interleukin-6(34.7%). Treatment include Intravenous Immunoglobulin and Steroids in 21(91.3%) patients. Sixteen (69.5%) children needed Inotrope supports .Mortality (26%) was high in children tested Covid 19 positive.

Conclusion: - MIS-C is an entity associated with Covid 19 in Pediatric population which needs early recognition and timely intervention, in order to prevent mortality.

KEYWORDS : Multisystem Inflammatory Syndrome ,Immunomodulators , Covid 19.

INTRODUCTION:-

The Corona virus disease 2019 (CoViD-19) has caused an upheaval in health system worldwide. Children and adults are equally vulnerable to infection of SARS-COVID-2 but symptomatic COVID-19 primary infection was significantly less and rarely causes severe disease in children. (1-3) In April of 2020, pediatricians in the United Kingdom reported a cluster of children with combination of Cardiogenic shock, fever and signs and symptoms of hyper-inflammation. (4) Maximum cases were noted after 4-6 weeks of peak of COVID-19 cases. This hyper inflammatory condition was labelled as Multi-system Inflammatory Syndrome in Children (MIS-C) associated to COVID-19. 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.

CRITERIA FOR MIS-C GIVEN BY CDC (7)

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Though rare but MIS-C Can be proven life threatening if timely recognition and aggressive management is not done.(6,7) There is paucity of data on the clinical presentation, laboratory parameters and treatment outcomes due to varied spectrum of MIS-C presentation.(6)

MATERIALAND METHOD:-

This was an observational study conducted at Balchikitsalya, Maharana Bhupal Government Hospital – a Tertiary care hospital in Southern Rajasthan India.

After clearance from the institutional Ethical Committee, the study was conducted from April 2021 to July 2021. Children of age <18 years admitted in this hospital and who were fulfilling the MIS-C definition proposed by Centre of Disease Control and prevention (CDC) were enrolled in this study. All above admitted children were subjected to detailed history regarding clinical course of disease and any history of contact with COVID positive or suspected case. In addition to this all those children were tested for ICMR based COVID RTPCR, Rapid Antigen Test by XaminR Covid 19 Antigen kit and Serology for COVID Antibodies by Electrochemiluminesce method. A pre designed proforma which included initial symptoms and clinical signs, laboratory parameters, drugs intake , symptom resolution duration, need for inotropic support, need of respiratory support in the form of invasive and non-invasive ventilation and mortality.

Initially the suspected patients were subjected to tier 1 investigations which includes COVID RTPCR,Serology, Complete Blood Count, Liver Function Test, Electrolytes and CRPQ. If tier-1 investigations and history were strongly suggestive of Multisystem involvement then they were further investigated for inflammatory markers like D-Dimer, Interleukin-6, serum ferritin, etc. Simultaneously treatment was initiated according to current gudelines recommended by Ministry of health and Family Welfare (MoHFW)(8). All data were analysed stastically using Microsoft Excel chart sheet, Windows 10.

RESULTS:-

A total of 23 children of less than 18 years of age with MIS-C who fulfilled CDC criterion of MIS-C ,were enrolled in this study for period of April 2021 to July 2021. The male female ratio was 1.09:1 and the median age was 7.07 years. Maximum number of children in age group 1to 5 years.[table 1]

Table 1:-Age And Gender Distribution

Age group	Males	Females
Birth to 1month	0	0
1month - 1 year	0	2
1 - 5 years	5	5
5- 10 years	4	2
>10 years	3	2
Total	12	11

Epidemiological inference noted that 17(70.8%) children had contact with family member having SARI like symptoms, among them 11(47.8%) member was COVID RTPCR positive. Those children who had contact with confirmed case had severe clinical sign on admission and had rapid clinical deterioration. (Table 4)

The result of ICMR based COVID RTPCR was positive in 6 (26%) patients. The serology for Anti COVID IgG was positive 23 (100%) patients. No patient had Rapid Antigen test positivity. All patients who were RTPCR Positive were critical and had grave prognosis. (Table 4) Out of 23 patients most common presentation on admission was fever> 3days (100%) followed by Gastrointestinal symptoms 95.6%, Hypotension 69.5% and Mucocutaneous Rashes (56.5%). Clinically Multiorgan involvement was seen in majority of children (69.5%). Most affected system was Gastrointestinal system(95.6%)followed by Respiratory system (33.3%) and Cardiovascular involvement (21.7%). [table 2]

Table 2:- Clinical Features On Admission In Childern With MIS-C (n=23)

Signs and symptoms	N(%)
Fever >3 days	23(100%)
Gastrointestinal symptoms	22(95.6%)
Hypotension	16(69.5%)
Mucocutaneous rashes	13(56.5%)
Conjunctivitis	9(39.1%)
Respiratory involvement	8(34.7%)
Cardiac (myocarditis)	5(21.7%)
Neurological (stroke)	2(8.6%)
Renal involvement	1(4.3%)

Table: - 3 Profile Of Lab Markers In Childern With MIS-C

LAB MARKERS	N (%)
Elevated CRPq	19 (82.6)
Elevated D-dimer	12(52.1)
Hypoalbuminemia	12(52.1)
Hyponatremia	12(52.1)
Neutrophilia	11(47.8)
Lymphopenia	8(34.7)
High ferritin	10(43.4)
Thrombocytopenia	9(39.1)
Abnormal chest xray	8(34.7)
Abnormal 2d Echo	5(21.7)

C reactive protein (>20mg/L); D dimer (500ng/ml); Hypoalbuminemia (<3.5g/dl); Hyponatremia (<135meq/l); neutrophilia (7500/mm3); lymphopenia (<1500/mm3); ferritin (>500ng/ml), thrombocytopenia (<1.5lac/mm3); abnormal 2D echo showimg minimal pericardial effusion and myocarditis.

Lab parameters analysis showed that CRP-q was elevated in majority (82.6%) of children ((IQR-45.25{51.25 -96.5}). Elevated D-dimer was found in 52.1% patient with (IQR-2475{2300-6775}). Elevated N:L ratio was seen in 47.8% patients.(Table 3)

Among the 23 Childern, 21(91.3%) were treated with Intravenous Immunoglobulins and Steroids(Methylpredenisolone) both and only 2 (8.6%) receieved Steroids alone. As Hypotension was striking feature on admission , 13(56.5%) patients needed fluid therapy and ultimately Inotrope supports .Low molecular weight Heparin ,Enoxaparin was given to 12(52.1%) patients where d-dimer was elevated.

Table:-4 Mortality And Morbidity Profile Of MIS-C Children

Parameters	NO. of Patients	RTPCR POSITIVE N=6	H/O RTPCR CONFIRMED CONTACT N=11
HYPOTENSION	16	6/16	11/16
INOTROPIC SUPPORT	13	6/13	11/13
ARDS	8	6/8	8/8
HFNC	12	6/12	8/12
MECHANICAL VENTILATION	8	6/6	8/8
STROKE	1	1/1	1/1
AKI	1	1/1	1/1
IVIG USED	21	6/21	11/21
PULSE THERAPY STEROID	6	6/6	3/6
COMORBIDITY	5	5/5	1/5
MORTALITY	6	6/6	6/6

Our analysis from Table 4 concluded that ,those Children who had contact with RTPCR positive family member were critical on admission. These all children presented with Hypotension and needed Inotrope support . Among these children, 8 (72.7%) also had Acute respiratory distress syndrome and required invasive ventilation.

Six children who were COVID RTPCR positive had contact with positive family member with a lag period of 2-3weeks. These six children had rapid clinical deterioration and among these, four patients had co morbid severe malnutrition aged between 1to 5 year and one patient had underlying heart disease . In our study series 6(26%) patient died and 17(73.9%) discharged.

One RTPCR Positive patient aged 16 years with no comorbidity had contact with COVID Positive father presented with stroke had rapid clinical deterioration.

DISCUSSION:-

This Study describes the Clinical profile of MIS-C in Southern Rajasthan and the data were consistent with studies done in Europe and US ,where clinical profile mimicking the Kawasaki like illness and toxic shock syndrome.(9,10)

As in a study from New York, MIS-C cases in State followed the peak of the Covid-19 epidemic, which supports a Temporal and Geographic association between Covid-19 and MIS-C(6). In the Southern Rajasthan the Second peak of COVID 19 cases reported in March and April 2021. In April 2021, children with active COVID-19 infection were reported with fever, gastro-intestinal symptoms(severe diarrhoea and vomiting) and severe shock. Therefore, they required inotropes and ventilator support. Children who had Hyperinflammatory syndrome during active infection along with comorbidities like Heart disease, pneumonia and malnutrition had poor outcome.

After the 4-6 weeks of second peak of COVID-19 in May 2021 – June 2021, our paediatric isolation ward witnessed case of Kawasaki disease like illness like fever> 3 days, skin rash, conjunctivitis, shock and various organ involvement. Similar association was estabilished in our study where majority 70.8% of children had febrile Inflammatory response after positive contact with SARS CoV 2.

In this study we evaluated 23 children fulfilling MIS definition proposed by CDC,with male to female ratio 1.09:1. Most series have reported involvement of children above 6 years(6,10,11,12) . However, in our study majority of MIS children were 1 to 5 years(43.4%).

Fever was most common presentation in our as well as study done by Dufort et al, Dhanlakshmi et al ,Ahmed et al(9,13,14). A meta analysis done by Ahmed et al (14) showed Gastrointestinal Manifestation in 73.1% and Mucocutaneous involvement in 50% children .In our study GI symptoms were present in 95.6 % and rashes in 56.6% children. [TABLE 2] Dhanalakshmi et al. (14) in his study of 19 Indian children had higher incidence of Mucocutaneous invovement than GI symptoms.

Although, Cardiac dysfunction is the most commonly reported organ dysfunction. [10,11,15], In our study we found, lesser number of chlidren had cardiac involvement 21.7% in 2-d Echo . Sixteen children(69.5%) presented with Hypotension , among which 5(31.2%) had carditis findings on echocardiography [Table2].Similar to this Dhanlakshmi et al (14) also repoted higher patient admitted with Hypotension(57.1%).

In a view of raised inflammatory markers in our study ,CRPq was elevated in 82.6% of patient with IQR45.25[51.25 -96.5] , which was a consistent with finding in other Indian studies done by Dhanlakshmi et al(13) Chattopadhyay et al (9) showed raised CRPq in 100% with median CRPq IQR 118[73-298] and 217[128-307] respectively.

In our study group CBC showed Neurtophilia in11(47.8%) Thrombocytopenia in 9 (39.1%) with raised N:L ratio(34.7%) ,Chattopadhyay et al(16) also reported Neurophilia(70.5%), Thrombocytopenia(64.5%) and raised N:L ratio (23.2%).

Whitker et al ,Dufort M et al (9,11) descriebed that children presenting with shock had high levels of inflammatory markers and required inotrope supports on admission . A cohort study on MIS-C in New York by Dufort et al(11) reported myocarditis in 53%, shock in 10% and coronary aneurysm in 9%. Recently Dhanalakshmi et al(13) also studied children of MIS from Chennai india ,reported hypotension treated with vasoactive medication in 57% of patients and coronary artery changes in 16%.

Whitker et al,Dufort et al also observed that myocarditis and coronary involvement had lead to shock requiring inotrope support.(11,9) These conclusions and findings were consistent with our study, Hypotension was present in 16/23 (56.5%) patient and needed Inotrope support in 12 patients ,however Echocardiographic findings of myaocarditis were seen in five (21.7%) of our patients.

In our study, we used IVIG and Steroids in 21(91.3%) children along with supportive treatment . Children presented with Acidosis and Hypotension required high doses of IV Steroids and 2 pateints needed repeat dose of IVIG. As we encountered abnormal coagulation profile and there were evident Thrombocytopenia aspirin was not prescribed. Enoxaparin was prescribed in 52% patients. Whitker et al ,Dufort et al conducted a study in UK and US where they used Intravenous Immunoglobulins 65% and 71% and systemic Steroids in 95% and 64% respectively.(11,9)

The mortality in children with Covid infection in study by Hoang et al in 7780 pediatric patient, has been observed to be 0.09%(17), while in those with MIS-C it ranges between 1.7–11%(11,14). Whittaker et al. reported in their study of 58 children, 29 (50%) patients required intensive care unit admission, mechanical ventilation required in 43% and 1 patient expired(11). The mortality in particular cohort is multifactorial, varies with pre-existing comorbidity and demographic profile. The mortality profile in our study was 26% (6/23) ,among this 3 were males .These Six children were RTPCR positive as well as they had IgG antibodies for SARS CoV 2. We found that in our mortality proportion , severe malnourishment was contributing factor, as our 4/6 patients were severely malnourished and one had underlying heart disease,though we had limited number of cases.

Previous studies concluded that there is 2-4 week post Covid lag period in cases of MIS-C.So ,we should suspect MIS-C if this Febrile Hyperinfammatory cases in children continue to rise . The Immunomodulatory treatment for MIS-C showed promising role in decreasing the morbidity and mortality profile.

CONCLUSION:-

In our study, we collected data on clinical characteristics and lab profile. High suspicion of MIS-C in patients with fever, inflammation, shock and raised inflammatory markers lead to early diagnosis and prompt treatment with steroids and IVIg which resulted into favourable outcomes. We concluded from our study that, children who were RTPCR positive and had contacted with positive family member were more critical on admission, had rapid clinical deterioration and had poorer prognosis. In our study comorbid condition like severe malnutrition and heart disease were main contributory factor for mortality.

Limitation:

1.The serological titre against SARS COV2 were qualitative ,otherwise we can estabilished correlation of disease severity with quantitative analysis of antibody titre. 2. the coronary artery involvement, Z Score could not be analysed by our 2d Echocardiography 3. The CDC criterion of MIS-C includes up to age 21 years , but our isolation ward admission age limit is up to 18 years.

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