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Unraveling The Role Of Inflammatory Markers In Multisystem Inflmmatroy Syndrome – A Comaparative Analysis In A Tertiary Care Hospital Of Southern Odisha

Dr Prachi Jena[1], Dr Devi Prasad Pradhan[2], Dr Bishnupriya Panda[3], Dr Subrat Kumar Pradhan[4]
[1]Assistant Professor, Department of Biochemistry, IMS and SUM Hospital, Kalinga Nagar, Ghatikia, Bhubaneswar, Odisha, India
[2]Associate Professor, Department of Biochemistry, GMCH Sundargarh, Odisha, India
[3]Assistant Professor, Department of Biochemistry, MKCG MCH, Berhampur, Odisha, India
[4]Senior Resident, Department of Biochemistry, MKCG MCH, Berhampur, Odisha, India

ABSTRACT

Background: *Multisystem inflammatory syndrome (MIS) is a rare and serious complication of COVID-19 that can affect different parts of the body. It can affect both children (MIS-C) and adults (MIS-A). MIS occurs in patients with pathophysiology characterised by hyperinflammation affecting multiorgan systems like gastrointestinal, renal, and cardiac involvement. The common presentation of fever, rash, headache, and sore throat are seen in acute covid patients. MIS in adults is complicated by the occurrence of hyperinflammation due to COVID 19 which presents with even broader spectrum of inflammatory markers which mimics other multisystem inflammatory disease like Kawasaki disease, toxic shock syndrome, macrophage activation syndrome. So, it is very important to diagnose the MIS and categorise whether the MIS is due to covid 19 or any other illness where the presentation is almost similar. Inflammatory markers play a major role is diagnosis and assessing the severity in MIS. In the present study, it was mainly aimed to estimate and compare the quantitative level of inflammatory markers in acute covid and MIS patients having positive and negative RTPCR for COVID 19. Hence the objective of a better diagnostic and predictive value can be elucidated by advising the healthcare facilities to go for assay of inflammatory markers along with observation of clinical manifestation and illness progression.*

Methods: *This retrospective observational study was carried out in Biochemical laboratory of MKCG Medical college and hospital in association with department of Medicine and Paediatrics from January to April 2023 which included 88 patients out of which 44 patients were diagnosed as acute covid (Group I),18 patients were MIS with RTPCR negative for covid virus (Group II) and 26 patients were MIS with positive RTPCR for covid virus (Group III).The serum sample for CRP(Q), Ferritin and D-Dimer were measured by immunoturbidimetry assay in MISPA i3 protein analyser. The serum sample was used for analysis of FBS, urea, creatinine, SGPT, SGOT and LDH by colorimetric method in automated analyser in TBA120FR.*

Results: *The level of serum urea, creatinine, SGPT, SGOT, LDH and inflammatory makers CRP(Q), Ferritin and coagulation marker D-Dimer were higher in MIS with RTPCR positive for covid (Group III) than the other two groups which was statistically significant ($p<0.001$)*

Conclusion: *Inflammatory markers and coagulation markers play a major role in recognising and treating the cases of MIS and in the present study it was very clear that the level of inflammatory and coagulation marker was significantly higher in MIS having COVID RTPCR positive as compared to MIS with COVID RTPCR negative but the levels were not elevated in acute covid.*

Key-words: *Multisystem inflammatory syndrome, Hyperinflammation, toxic shock syndrome, Kawasaki disease*

INTRODUCTION:

Multisystem inflammatory syndrome (MIS) is an eclectic disease having a spectrum of disease in children and adults (1). MIS occurs in patients with pathophysiology characterised by hyperinflammation affecting multiorgan systems like gastrointestinal, renal, and cardiac involvement (2). Kawasaki disease, macrophage activating syndrome, toxic shock syndrome, infection with adenovirus, enterovirus, Epstein Barr virus, Human herpes virus 6, rubeola are some of the causative agents of MIS (1,2). MIS in children (MIS-C) was newly described after SARS COV-2 infection on exposure in children which was reported in 2020. These children presented with fever, shock, cardiac involvement and multiorgan failure with rise

in inflammatory markers (3). MIS in adults (MIS-A) is a multi-inflammatory syndrome following covid 19 suggested to result from delayed dysregulated immune response (3). MIS-V is multi-inflammatory syndrome following vaccination of covid 19 without prior covid 19 infection or exposure (4).The US Centres for Disease Control and Prevention (CDC) criteria for diagnosing multisystem inflammatory syndrome defining a MIS-C includes an individual less than 21 years presenting with fever, having laboratory evidence of inflammation, clinical evidence of multisystem organ involvement with no plausible alternate diagnosis and a positive result for current or recent SARS COV 2 infection by RTPCR (5). The MIS-C definition excepting the age criterion which is age more than 21 years presenting with fever was applied for diagnosis of MIS-A (2).

The common presentation of fever, rash, headache, and sore throat are seen in acute covid patients. MIS in adults is complicated by the occurrence of hyperinflammation due to COVID 19 which presents with even broader spectrum of inflammatory markers which mimics other multisystem inflammatory disease like Kawasaki disease, toxic shock syndrome, macrophage activation etc. Kawasaki disease is known to occur in children under the age of 5 years, however the older patients are known to be more severe than younger. Toxic shock syndrome is potentially a lethal disease that occurs due to release of bacterial toxins that also depicts similarities with MIS due to covid. A diagnosis of MIS due to covid can be made by better characterization and assessment of laboratory markers as the clinical manifestations and illness progression are nearly same as other multisystem inflammatory disease (6).

So, it is very important to diagnose the MIS and categorise whether the MIS is due to covid 19 or any other illness where the presentation is almost similar. Inflammatory markers play a major role is diagnosis and assessing the severity in MIS. Hence in the present study, it was mainly aimed to estimate and compare the quantitative level of inflammatory markers in acute covid and MIS patients having positive and negative RTPCR for COVID 19. Hence the objective of a better diagnostic and predictive value can be elucidated by advising the healthcare facilities to go for assay of inflammatory markers along with observation of clinical manifestation and illness progression.

OBJECTIVES

- To estimate the serum levels of CRP(Q), Ferritin, D-dimer, LDH in suspected cases of Multi inflammatory syndrome and acute covid cases.
- To compare the serum level of the above inflammatory markers between the respective groups.

MATERIALS AND METHOD

This clinical study is a retrospective observational study that includes descriptive research work, from clinical and laboratorial data obtained from patients with suspected MIS from different sources and acute covid patients. This study was carried out in Biochemical laboratory of MKCG Medical college and hospital in association with department of Medicine and Paediatrics from January to April 2023. The study was approved by institutional ethics committee of the college [IEC NO.1364/2023].

Sample grouping:

A convenient purposeful sampling of 88 patients was included in the study comprising both adolescents and adults of age group 15 to 65 years. Out of 88 patients,44 patients were diagnosed as acute covid (Group I),18 patients were MIS with RTPCR negative for covid virus (Group II) and 26 patients were MIS with positive RTPCR for covid virus (Group III).

The acute covid patients were admitted in Dedicated Covid Hospital (DCH) working under MKCG Medical College. The diagnosis was made by physicians posted in DCH during the study period. The suspected MIS patients were admitted in department of Paediatrics and Medicine and were diagnosed as per MIS-C criteria according to CDC excepting the age criterion. [Figure/Table No: 1]. The test for RTPCR for Covid were sent on the day of admission. The suspected MIS cases were divided depending upon their RTPCR report.

Figure/Table no.1: Criteria for diagnosis of MIS-C according to CDC. (5)

• Age less than 21 years old.
• Fever more than equal to 38℃ for 24 hours.
• Laboratory evidence of inflammation by assessing more than one inflammatory parameter.

- Evidence if clinically severe illness requiring hospitalization with multisystem organ involvement.
- No alternate plausible diagnosis
- Positive for COVID-19 infection by RT-PCR, Antigen or Antibody test; or exposure to COVID-19 case within 4 weeks prior to the onset of symptoms.

METHODOLOGY:

The demographic parameters and data regarding clinical parameters and vaccination status of the patients were obtained from records of DCH and indoor wards of Paediatrics and Medicine departments. The blood samples were collected in the wards after receiving informed consent for the patients. The citrate vials were used to collect blood for D-dimer and plain vial was used for collection of blood for other inflammatory parameters. All the samples were collected between day 1-3 of admission. The blood samples received in biochemical lab was subjected to centrifugation at 4000 rpm for 10 minutes at room temperature. The plasma was separated from citrate vials and serum was separated from plain vial and stored at -20° C till further analysis. The serum sample for CRP(Q), Ferritin and D-Dimer were measured by immunoturbidimetry assay in MISPA i3 protein analyser. The serum sample was used for analysis of FBS, urea, creatinine, SGPT, SGOT and LDH by colorimetric method in automated analyser in TBA120FR. The normal levels of the parameters are tabulated in the Figure/Table 2.

Table/figure 2: Normal levels of the parameters (7)

Parameters	**Normal levels**
FBS	70-100 mg/dl
UREA	15-40 mg/dl
CREATININE	0.6-1.1 mg/dl
SGPT	5-40 U/L
SGOT	5-40 U/L
CRP	<6 mg/L
FERRITIN	10-291 ng/ml
D-DIMER	<0.5µg/ml
LDH	250-450 mg/dl

Statistical Analysis:

The data analysis was done using SPSS 25. We have used simple descriptive statistics and expressed continuous data as mean and standard deviation. The inflammatory parameters were compared using mean and standard deviations of all the three groups. A 'p' value of less than 0.05 was considered statistically significant.

RESULTS:

There were 88 patients enrolled in our study between January to April 2023. Out of these, 44 patients were diagnosed as Acute covid and grouped as Group I, 18 patients were diagnosed as MIS with RTPCR negative for covid and grouped as Group II and 26 patients were diagnosed as MIS with RTPCR positive for covid and grouped as Group III. The mean age of study subjects enrolled were from 15-65 years with mean age of 31.09 ± 13.38 years. There were 68.75 % male and 31.25% female patients. In this study, we estimated the inflammatory markers in all the three groups and compared the results with respective groups. The level of serum urea, creatinine, SGPT, SGOT and inflammatory makers CRP(Q), Ferritin, D-dimer and LDH were higher in MIS with RTPCR positive for covid (Group III) than the other groups which was statistically significant. (Figure/Table no 4 & 5)

Figure/Table 3: Table enumerating vaccinations status of the cases

	Total number of cases(n=88)	Number of vaccinated persons	Number of COVID 19 cases post vaccination
ACUTE COVID	44	32(72.7%)	4

MIS WITH RTPCR Negative	18	12(66.6%)	0
MIS WITH RTPCR Positive	26	18(69.2%)	2

Figure/Table No. 4: Comparison of Biochemical parameters in all the respective groups

	ACUTE COVID	**MIS WITH RTPCR Negative**	**MIS WITH RTPCR Positive**	**'p' VALUE**
FPS (mg/dl)	124.2 ± 30.7	115.1±20.0	127.1± 18.2	0.591
UREA (mg/dl)	30.5 ± 10.2	35.6±7.2	48.3±2.7	<0.001**
CREATININE (mg/dl)	0.65 ± 0.11	0.83±0.06	1.11±0.44	<0.001**
SGPT (mg/dl)	32.6 ±10.0	37.9±9.0	58.1±11.2	<0.001**
SGOT (mg/dl)	37.5 ±10.8	52.2±20.1	75.3±6.3	<0.001**

p<0.05 significant.

Figure/Table no.5: Comparisons of inflammatory markers in all the respective groups.

	ACUTE COVID	**MIS WITH RTPCR Negative**	**MIS WITH RTPCR Positive**	**'p' VALUE**
CRP (mg/L)	9.6±3.3	59.4±20.4	199.8±36.8	<0.001**
FERRITIN (ng/ml)	253.7±109.3	512.5±220.1	907.4±146.8	<0.001**
DDIMER (µg/ml)	1.04±0.48	2.6±2.4	3.3±1.0	<0.001**
LDH (mg/dl)	278.8±104.2	822.3±104.2	1403.6±392.4	<0.001**

p<0.05 significant.

DISCUSSION:

Multisystem inflammatory syndrome represents a potentially life-threatening complication following infection with COVID-19, the pathophysiology of which is yet to be fully understood. The syndrome was first described in APRIL 2020 in children called MIS-C and later similar cases began to appear in adults called MIS-A (8). SARS COVID 19 belongs to the coronavirus family that can present as common cold to manifesting a fatal pneumonia, which may progress to affect multi organs (9). This results due to the autoimmune response resulting from cross reactivity of viral and host antigens that cause release of cytokines and inflammatory markers in the body, which can predict the prognosis of the MIS due to covid (1,10). The are other disease which also cause multiorgan inflammatory response in the body which can mimic the covid presentations. The most commons are sepsis, toxic shock syndrome, macrophage activating syndrome and Kawasaki disease in children. These may cause diagnostic uncertainty for physicians and possess a challenge also (6).

In the present study, it was found that the inflammatory markers (CRP, LDH, Ferritin) and D-Dimer were significantly highly increased in MIS cases with RTPCR positive for covid than the other two comparative groups and this finding is in accordance with Sidhwani et al, as they also found out significant increase of same inflammatory markers with progression of disease (4).Several meta-analysis have also found that post-acute covid cases develop MIS with significant increased levels of acute phase reactants and biochemical levels of transaminases as observed in the present study (11,12,13,14).Mazumder et al. and Kobe et al. described cases of MIS-A with development of disseminated intravascular coagulopathy (DIC) and in the present study the high level of D-Dimer may give an explanation for the possible development of DIC in MIS(15,16,17). It was also found that the cases with MIS with RTPCR negative for covid, have higher inflammatory marker levels than acute covid cases. This suggest that MIS can also be due to other above-mentioned causes, out of which most common cause is sepsis. Since acute covid is defined as initial phase of onset of disease which presents with fever, rash, sore throat and evidence of recent infection with covid 19 through positive RTPCR; the level of inflammatory markers is not high as MIS groups. (10,18)

Four cases developed acute covid after vaccination and 2 cases developed MIS with RTPCR positive for covid after vaccination as observed in this study. The higher inflammatory marker in these cases suggest that MIS can occur after vaccination so categorising them into MIS-V. Zambrano et al, in their report found protective effect after complete two dose of Pfizer vaccine. When Phase 2 and Phase 3 trials were complete, they found no case of MIS-V (19). In this study, the number of cases with MIS-V were very low. Therefore, this suggests that, there is low likelihood of vaccine induced development of MIS. Jain et al, reported two cases of successfully treated MIS-V with one case having history of previous community acquired covid infection (20). Elsaid et al, in their systematic review have suggested three possible ways of acquiring MIS-V. Firstly, following covid vaccination without prior covid infection. Secondly, in those persons who had prior covid infection and then got vaccinated. Thirdly, MIS can develop in person who are vaccinated then contract covid on exposure to community and present with features of MIS after 4-6 weeks. (21)

Multisystem inflammatory syndrome in non-covid patients may be due to sepsis, toxic shock syndrome, certain viral infection like adenovirus, enterovirus and herpes virus and Kawasaki disease in children. All these share related features with covid such as fever, rash, sore throat, abdominal pain and vomiting (6,22). The gastrointestinal symptoms are very common in children with MIS due to covid which is not seen in TSS and Kawasaki disease. Respiratory distress in mostly seen in adults when compared to children in MIS due to covid which may overlap in other hyperinflammatory conditions leading to MIS (23). In our study we found, MIS due to non-covid causes have increased level of inflammatory markers which is very significant when compared to acute covid cases but MIS due to covid have higher inflammatory marker level than MIS due to non-covid causes. This may suggest that massive proinflammatory state of acute covid may lead to MIS due to covid. (24)

To have good differential diagnosis between the above kinds of MIS, the estimation of inflammatory parameters has a major role. This helps in better prognosis and treatment plan of the patients. The MIS cases due to covid are better treated with IVIg and steroids with symptomatic management (25). But in other cases of MIS due to non-covid causes, the most common being sepsis, can be treated with simple intravenous antibiotics.

CONCLUSION:

MIS represents a severe form of dysregulated immune response of the host which might be either due to SARS-COV-2 virus or due to sepsis, toxic shock syndrome and some unrecognised MIS having a very high mortality rate, and for this very reason, it very important to diagnose, categorise and treat promptly when MIS is suspected. Inflammatory markers and coagulation markers play a major role in recognising and treating the cases of MIS and in the present study it was very clear that the level of inflammatory and coagulation marker was significantly higher in MIS having COVID RTPCR positive as compared to MIS with MIS having COVID RTPCR negative but the levels were not elevated in acute covid.

LIMITATIONS:

The sample size was less and larger sample size is required to find out the other causes of MIS other than covid-19. Other inflammatory marker like IL-6, TNF-alpha, procalcitonin and coagulation markers and cardiac markers were not evaluated in this study.

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