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Original Research Paper

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COMPARISON OF CLINICO-LABORATORY PROFILE AND OUTCOME IN MULTISYSTEM INFLAMMATORY SYNDROME AND DENGUE INFECTION IN CHILDREN AND IN A TERTIARY CARE CENTER.

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ABSTRACT

Objective: To identify clinical and laboratory features that distinguish children with dengue fever from MIS-C and predict their outcomes. **Methods:** A retrospective study was done on children aged more than 1 month of age who presented to the pediatric department in a tertiary care hospital. Data was collected from case records of children admitted and diagnosed with Dengue/MIS-C from May 2022 to November 2022. A structured proforma was used to document clinical and laboratory data. **Results:** In this study, a total of 36 MIS-C cases and 54 Dengue cases were included. A mean age of 8.7 years was found in the Dengue group, while a mean age of 7.17 years was found in the MIS-C group. Children with MIS-C were younger than those with dengue fever (P=0.0027). Predominant complaint of abdominal pain was seen in dengue fever and headache in MIS-C . The mean C reactive protein level was higher in MIS-C children [5.26 vs 73.63 mg/dL] (P<0.001). In the MIS-C group, anemia was observed, while thrombocytopenia and leukopenia were seen in the Dengue group. As compared to the Dengue case group, the MIS-C case group had a longer length of PICU stay (3.03 vs 1.89; p <0.001) and hospital stay (8.64 vs 5.17 days; p<0.001). **Conclusions:** In order to diagnose MIS-C early and to distinguish it from dengue, clinical and laboratory parameters are required. Early initiation of appropriate treatment reduces mortality and morbidity.

KEYWORDS : MIS-C, Early diagnosis, Treatment, Reducing mortality

INTRODUCTION

Children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection often present with fewer and milder symptoms (Grimaud et al., 2020). However, there is growing concern about a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection((PIMS-TS)/ Multisystem inflammatory syndrome in children (MIS-C) (Toubiana et al., 2020).

Multisystem inflammatory syndrome in children (MIS-C) is a pediatric inflammatory multisystem syndrome which occurs weeks after SARS-CoV virus exposure (Grimaud et al., 2020). Clinical manifestations include high-grade fever, rash, conjunctival injection and gastrointestinal symptoms , myocardial dysfunction and cardiogenic shock (Feldstein et al., 2020).

Considering a number of tropical illnesses, such as dengue, scrub typhus, malaria, enteric fever, and leptospirosis, can present with overlapping clinical features, it is critical to use a broader syndromic approach early in the diagnostic and treatment process (Singhi et al., 2017). Dengue fever is characterized by biphasic fever with abdomen pain, thrombocytopenia, third space fluid loss, hypovolemic shock, and multiorgan dysfunction. The difficulty of detecting one of these conditions at admission may be increased by overlapping outbreaks. Furthermore, these disorders necessitate diverse management procedures, which may impede their outcome.

There are many similarities between MIS-C and severe dengue infection, except for the later onset of circulatory failure. There is a need to increase awareness, including the history of SARS-CoV-2 contact, early recognition of inflammatory signs and PCR or antigen testing to prevent misdiagnosis of MIS-C and delayed treatment (Yuliarto et al., 2021) .

Characterizing the epidemiology, spectrum of disease, clinical course, therapies, and prognosis of the disease is a crucial component in reducing MIS-C-related morbidity and death (Feldstein et al., 2020). A comparison of the epidemiological, clinical, and laboratory profiles of dengue and MIS-C would aid in the differentiation of both illnesses in children and assist doctors in arriving at a diagnosis from the start. Thus, the case records of children hospitalized with dengue and MIS-C were reviewed retrospectively, and their clinical-laboratory characteristics and outcome were compared (Randhawa Manjinder Singh et al., 2022).

METHODS:

Study Design:

A retrospective study was done on children aged more than 1 month of age who had presented to pediatric department in Ramaiah medical college and hospitals between January 2023 to March 2023 with fever for more than three days and fulfilling the World Health Organization (WHO) criteria for MIS-C and Government of India guidelines (GOI) for dengue infection (Ministry of Health and Family Welfare, 2008; World Health Organisation, 2020).

The diagnosis of dengue is based on the detection of the NS1 antigen or the presence of specific IgM anti-dengue 2 antibodies in an ELISA test (PANBIO KIT).

All children were tested for SARS-CoV-2 infection by detecting IgG antibodies against SARS-CoV-2 using the CMIA technique (ABBOTT KIT).

Data was collected from case records of children admitted and diagnosed with Dengue/MIS-C from May 2022 to November 2022. In a predesigned structured proforma, information of demography, clinical symptoms and signs were recorded. Initial(at admission) laboratory values such as total blood count, liver function tests [alanine aminotransferase(ALT), aspartate aminotransferase(AST), albumin] and renal function tests (BUN, urea, creatinine) were noted. Details of shock, fluid bolus, mechanical ventilation, inotropes therapy were recorded. Hospital outcomes such as length of stay in the pediatric intensive care unit (PICU),total hospital stay and mortality were recorded.

Statistical Analysis:
Sample size estimated based on the difference in proportion of rash between MISC and was 22.7% and in Dengue was 72.5% from the study by Manjinder singh et al. using these values in the below mentioned formula (Randhawa Manjinder Singh et al., 2022)

$$N = \frac{2(Z\alpha/2 + Z\beta)2P(1-P)}{(p1-p2)2}$$

Where ,
Z /2= Z0.05/2=Z0.025 = 1.96 at type 1 error of 5%
Z =Z0.20= 1.28= At 90% power
p1 –p2= Difference in proportion in the two different groups = 49.8%
P= Pooled prevalence = [Proportion in MISC (p1) + Proportion in Dengue (p2)]/2 = [22.7 + 72.5]/2 = 47.6
N = 23 in each group

Considering Non response rate of 10%, 23 + 2.3 = 25.3 ≈ 26 children will be included in each group.

The data was entered into a Microsoft Excel data sheet and analyzed with SPSS 22 software. Frequencies and proportions were used to represent categorical data. As a test of significance for qualitative data, the Chi-square test or Fischer's exact test (for 2x2 tables only) were utilised.

The mean and standard deviation were used to describe continuous data. The independent t test was employed as a statistical test to determine the mean difference between two quantitative variables.

Data Graphic Representation:
MS Excel and MS Word were used to generate several sorts of graphs. P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical Software:
MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

Table 1:- Age Wise Distribution Of Children With Dengue And MISC

	Dengue		MISC	
	N	%	N	%
<1yrs	9	16.7	4	11.1
1-5yrs	4	7.4	14	38.9
6-10yrs	19	35.2	6	16.7
>10yrs	22	40.7	12	33.3

P Value 0.0027 showed statistically significant

Table 2:- Gender Wise Distribution Of Children With Dengue And MISC

	Dengue		MISC	
	N	%	N	%
Female	17	31.5	14	38.9
Male	37	68.5	22	61.1

P Value 0.468, there was no statistically significant

Table 2: Symptoms In Children With Dengue And MISC

	Dengue		MISC		
	N	%	N	%	
Fever	54	100	34	94.4	0.328
Seizure	0	0	5	13.9	---
Rash	9	16.7	7	19.4	0.735
Conjunctival injection	3	5.6	6	16.7	0.085
Petechiae	1	1.9	0	0	---
Myalgia	2	3.7	3	8.3	0.347
Headache	2	3.7	5	13.9	0.077
Cold/Cough	3	5.6	0	0	---
Increased frequency of micturition	1	1.9	0	0	---
Pain abdomen	21	38.9	9	25.0	0.170
Vomiting	35	64.8	19	52.8	0.253
Malena	1	1.9	0	0	---
Epistaxis	2	3.7	0	0	----
Diarrhoea	6	11.1	5	13.9	0.69
Respiratory distress	3	5.6	4	11.1	0.335

Table 3: Distribution Of Signs In Children With Dengue And MISC

	Dengue		MISC		
	N	%	N	%	
Hepatomegaly	23	42.6	16	44.4	0.862
Splenomegaly	2	3.7	3	8.3	0.347
Shock at admission	4	7.4	3	8.3	0.872
Inotrope	8	14.8	6	16.7	0.81
PICU admission	33	61.1	18	50.0	0.297
NIV	0	0	6	16.7	---
Mortality	1	1.9	1	2.8	0.77

Table 4: Laboratory Parameters

	Mean	SD	Mean	SD	P Value
Hb (g/dl)	13.2481	1.80	10.65	1.80	<0.001
PCV%	39.89537	7.421	32.88	5.198	<0.001
TLC (cells/cumm)	4824.26	2456.898	11482.22	6524.0	<0.001
PLATELET COUNT (Lakh cells/cumm)	.62	.53	1.797222	1.567	<0.001
CREATININE (mg/dl)	.532593	.18	0.500	.239	0.490
TOTAL BILIRUBIN (mg/dl)	.405370	.194	.863056	1.23	0.008
DIRECT BILIRUBIN (mg/dl)	.200926	.1714232	.454722	.79	0.026
TOTAL PROTEIN (g/dl)	6.061111	.7814	6.15	.69	0.576
ALBUMIN (g/dl)	3.700	.463	3.42	.58	0.007
AST (U/L)	201.87	369.353	126.03	192.175	0.265
ALT (U/L)	106.17	138.876	80.17	85.684	0.315
CRP(mg/L)	5.26	9.08	73.63	63.37	<0.001

Table 5: Associated Morbidity

	Mean	SD	Mean	SD	P value
Age	8.7722	4.95469	7.1711	5.37383	0.167
Length of PICU stay	1.89	1.766	3.03	4.754	0.106
Length of hospital stay	5.17	1.539	8.64	4.297	<0.001
Duration B/w fever & Shock	1.04	2.577	5.22	2.489	<0.001

RESULTS:
Out of total 36 MIS-C cases, the majority 38.9% (n = 14) were between the ages of 1–5 years, and out of the 54 Dengue cases, 75.9% (n = 41) were above the age of 5 years. Males preponderance was seen in both the groups, MIS-C (n = 22; 61.1%) and dengue (n = 37; 68.5%) cases.

Fever was present in 94.4%(34 children) of MIS-C (n=34 ; 94.4%) while all(100%) children with dengue had fever. The most common prodromal symptoms related to MIS-C were myalgia, headache, conjunctival injection, and rash, while

dengue children suffered abdominal symptoms like pain and vomiting. The only clinical feature that was statistically significant was headache, more commonly seen in the MIS-C(n= 5; 13.9 %) subgroup with p = 0.077.

Hepatosplenomegaly was found more often in children diagnosed with MIS-C compared to those with dengue. There was a higher incidence of shock at admission and inotrope requirements for children with MIS-C than for those with dengue. The duration between fever and the onset of shock was 1 day for dengue whereas it was 5 days for the MIS-C group, which was statistically significant (p value 0.001).Children with MIS-C are more likely to experience respiratory distress requiring non-invasive ventilation.

Considering the date of discharge as the endpoint, MIS-C group had a significantly longer hospitalization (8 days) than dengue fever children (5 days) with statistically significant p value of 0.001. Children with MIS-C had a two-day longer average PICU stay than children with dengue.

Hemoglobin and PCV were found lower in children with MISC than Dengue which was statistically significant(p value of 0.001). Platelet count and total leukocyte (TLC) count were higher in the children with MISC than in dengue with a significant p value of 0.001.

Both groups showed elevated CRP but it was significantly higher in the MIS-C group (p value 0.001) and AST, ALT derangement was more common with the Dengue group.

DISCUSSION

The present study was conducted to study the differences in clinico-laboratory profile and outcome between Multisystem inflammatory syndrome-and Dengue in children in a tertiary care center.

Dengue fever was more common in older children than MIS-C, which affected children of a younger age. Similar results were seen in a study conducted by Dhooria GS et al. (9). Gender wise distribution showed no statistically significant difference between both groups(p value of 0.468). This is in contrast to a study by Roberts J et al in Boston who noted MIS-C to be affecting more of older and male children (Roberts et al., 2022).

Rash, conjunctival injection, myalgia, and headache were more frequently seen in children with MIS-C than in those with dengue. Children with dengue had more gastrointestinal symptoms, such as abdominal pain and vomiting. This contradicts the findings of the Randhawa MS et al. study, which concluded that gastrointestinal symptoms were more common in children with MIS-C (Randhawa Manjinder Singh et al., 2022). In cases of severe dengue, abdominal discomfort is a crucial early warning symptom (Karyanti et al., 2020; Pothapregada et al., 2016) .

Children with dengue had significantly higher hemoglobin levels at admission [13.2 vs. 10.6 g/dL ($p < 0.001$)] while platelets were markedly lower [62000 cells/mm^3 vs. 1.79 lakh cells/mm^3 ($p < 0.001$)].

Although both MIS-C and Dengue present with thrombocytopenia and leukopenia with lymphopenia. Differentiating the two is based on other laboratory values. A significant increase in CRP, ferritin, procalcitonin, BNP, and troponin is usually seen in MIS-C+ children. A higher ratio of neutrophils to lymphocytes as well as ferritin to CRP is observed in MIS-C+ children. An abnormal troponin level is commonly seen in MIS-C+ children (Roberts et al., 2022) . Total Leucocyte count was significantly lower in children with Dengue than in MIS-C [4824 vs 11482.2 cells/mm^3($p < 0.001$)]. CRP levels were noted to be on the significantly higher in children with MIS-C than with dengue[(73.3 vs 5.2 (p value < 0.001)]. In a studies conducted by Randhawa M et al, Carlin and Kelly et, similar results were obtained (Carlin et al., 2021; Kelly et al., 2021; Randhawa Manjinder Singh et al., 2022) . A study done by Dhooria GS et al. In their study inflammatory marker levels of CRP, IL-6, D dimer and fibrinogen were significantly higher in MIS-C when compared to dengue fever children (Dhooria et al., 2021).

A higher incidence of shock warranting inotropes for management was observed in MIS-C than in dengue. This was in accordance with a study done by Whittaker E et al. in the United Kingdom, where shock at admission was seen in 27 of the 58 children (46.5%) under study (Whittaker et al., 2020). However children who have recently been exposed to SARS-CoV-2 infection, dengue fever may progress less severely (Ravikumar et al., 2021). Length of hospital stay was more for children diagnosed with MIS-C with an average of 8 days against 5 days for children diagnosed with Dengue. In a study conducted by Roberts J et al in Boston in the year 2020-2021 noted a longer hospital stay for children confirmed with diagnosis of MIS-C (Roberts et al., 2022) .

Better discrimination of dengue and MIS-C helps us in early diagnosis. High index of suspicion of diagnosis helps in early initiation of appropriate treatment and reducing the morbidity and mortality (Dean et al., 2021). Due to the completely different therapeutic approaches for the two illnesses, it is critical to distinguish between dengue fever and MIS-C. Underdiagnosis and a delay in diagnosis might cause immunomodulatory therapy to be delayed, the inflammatory condition to persist, and organ dysfunction to worsen (Dean et al., 2021; Molloy et al., 2021) .

Children with dengue fever are treated aggressively with crystalloids, colloids, inotropic support, and platelet transfusions as necessary. On the other, such aggressive fluid would be harmful for MIS-C children with cardiac dysfunction. Early identification and prompt use of steroids and intravenous immunoglobulin in the treatment of MIS-C children cannot be overstated.

There are a couple of limitations to the study. It is a retrospective study with a small sample size from a single tertiary care hospital. The diagnosis of dengue was solely based on serology, which could have led to some MIS-C cases going undiagnosed. Inflammatory markers could not be compared in this study.

CONCLUSION

Rashes, conjunctival injection, myalgia, and headaches were more prevalent in MIS-C children than in dengue children. Dengue fever children reported increased gastrointestinal symptoms, such as nausea and vomiting. Dengue children had lower total leukocyte counts and platelet counts, although MIS-C children had substantially higher CRP levels. MIS-C was related with a greater incidence of shock, necessitating the administration of inotropes. Children with MIS-C had a more extended hospital stay than children with Dengue. Early identification of MIS-C vs dengue lowers mortality and morbidity by initiating appropriate treatment.

REFERENCES:

1. Carlin, R. F., Fischer, A. M., Pitkowsky, Z., Abel, D., Sewell, T. B., Landau, E. G., Caddle, S., Robbins-Milne, L., Boneparth, A., Milner, J. D., Cheung, E. W., Zachariah, P., Stockwell, M. S., Anderson, B. R., & Gorelik, M. (2021). Discriminating Multisystem Inflammatory Syndrome in Children Requiring Treatment from Common Febrile Conditions in Outpatient Settings. *Journal of Pediatrics*, *229*(e2), 26–32. https://doi.org/10.1016/j.jpeds.2020.10.013
2. Dean, A., Asaithambi, R., & Neubauer, H. C. (2021). Murine typhus in 5 children hospitalized for multisystem inflammatory syndrome in children. *Hospital Pediatrics*, *11*(4). https://doi.org/10.1542/HPEDS.2020-005652
3. Dhooria, G. S., Kakkar, S., Pooni, P. A., Bhat, D., Bhargava, S., Arora, K., Gill, K., & Goel, N. (2021). Comparison of Clinical Features and Outcome of Dengue Fever and Multisystem Inflammatory Syndrome in Children

Associated With COVID-19 (MIS-C). *Indian Pediatrics*, *58*(10), 951–954. https://doi.org/10.1007/s13312-021-2329-9

4. Feldstein, L. R., Rose, E. B., Horwitz, S. M., Collins, J. P., Newhams, M. M., Son, M. B. F., Newburger, J. W., Kleinman, L. C., Heidemann, S. M., Martin, A. A., Singh, A. R., Li, S., Tarquinio, K. M., Jaggi, P., Oster, M. E., Zackai, S. P., Gillen, J., Ratner, A. J., Walsh, R. F., … Randolph, A. G. (2020). Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine*, *383*(4), 334–346. https://doi.org/10.1056/nejmoa2021680
5. Grimaud, M., Starck, J., Levy, M., Marais, C., Chareyre, J., Khraiche, D., Leruez-Ville, M., Quartier, P., Léger, P. L., Geslain, G., Semaan, N., Moulin, F., Bendavid, M., Jean, S., Poncelet, G., Renolleau, S., & Oualha, M. (2020). Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Annals of Intensive Care*, *10*(1). https://doi.org/10.1186/s13613-020-00690-8
6. Karyanti, M. R., Uiterwaal, C. S. P. M., Hadinegoro, S. R., Jansen, M. A. C., Heesterbeek, J. A. P. H., Hoes, A. W., & Bruijning-Verhagen, P. (2020). Clinical Course and Management of Dengue in Children Admitted to Hospital: A 5 Years Prospective Cohort Study in Jakarta, Indonesia. *Pediatric Infectious Disease Journal*. https://doi.org/10.1097/INF.0000000000002479
7. Kelly, M. S., Fernandes, N. D., Carr, A. V., Lahoud-Rahme, M., Cummings, B. M., & Chiu, J. S. (2021). Distinguishing Features of Patients Evaluated for Multisystem Inflammatory Syndrome in Children. *Pediatric Emergency Care*, *37*(3), 179–184. https://doi.org/10.1097/PEC.0000000000002344
8. Ministry of Health and Family Welfare, G. (2008). *National Centre for Vector Borne Disease Control, Ministry of Health and Family Welfare, GOI. Guidelines : National Vector Borne Disease Control Programme (NVBDCP)*. Ministry of Health and Family Welfare, GOI. https://nvbdcp.gov.in/index1.php?lang=1&level=1&sublinkid=5851&lid=3686
9. Molloy, M., Jerardi, K., & Marshall, T. (2021). What are we missing in our search for mis-c? *Hospital Pediatrics*, *11*(4). https://doi.org/10.1542/HPEDS.2020-005579
10. Pothapregada, S., Kamalakannan, B., Thulasingham, M., & Sampath, S. (2016). Clinically profiling pediatric patients with dengue. *Journal of Global Infectious Diseases*, *8*(3). https://doi.org/10.4103/0974-777X.188596
11. Randhawa Manjinder Singh, Angurana Suresh Kumar, Nallasamy Karthi, Kumar Mahendra, Ravikumar Namita, Awasthi Puspraj, Ghosh Arnab, Ratho R K, Minz Ranjana W, Kumar Rohit Manoj, Bansal Arun, & Jayashree Muralidharan. (2022). Comparison of Multisystem Inflammatory Syndrome (MIS-C) and Dengue in Hospitalized Children. *Indian J Pediatr.*, 1–6.
12. Ravikumar, N., Randhawa, M. S., Nallasamy, K., Angurana, S. K., Kumar, M., Mohi, G. K., Ratho, R. K., & Jayashree, M. (2021). Impact of recent SARS-CoV-2 infection on the course and severity of dengue in children: A prospective observational study from North India. *American Journal of Tropical Medicine and Hygiene*, *105*(3). https://doi.org/10.4269/ajtmh.21-0586
13. Roberts, J. E., Campbell, J. I., Gauvreau, K., Lamb, G. S., Newburger, J., Son, M. B., & Dionne, A. (2022). Differentiating multisystem inflammatory syndrome in children: A single-centre retrospective cohort study. *Archives of Disease in Childhood*, *107*(3), e3. https://doi.org/10.1136/archdischild-2021-322290
14. Singhi, S., Rungta, N., Nallasamy, K., Bhalla, A., Peter, J. V., Chaudhary, D., Mishra, R., Shastri, P., Bhagchandani, R., & Chugh, T. D. (2017). Tropical fevers in Indian intensive care units: A prospective multicenter study. *Indian Journal of Critical Care Medicine*, *21*(12), 811–818. https://doi.org/10.4103/ijccm.IJCCM_324_17
15. Toubiana, J., Poirault, C., Corsia, A., Bajolle, F., Fourgeaud, J., Angoulvant, F., Debray, A., Basmaci, R., Salvador, E., Biscardi, S., Frange, P., Chalumeau, M., Casanova, J. L., Cohen, J. F., & Allali, S. (2020). Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ (Clinical Research Ed.)*, *369*, m2094. https://doi.org/10.1136/bmj.m2094
16. Whittaker, E., Bamford, A., Kenny, J., Kaforou, M., Jones, C. E., Shah, P., Ramnarayan, P., Fraisse, A., Miller, O., Davies, P., Kucera, F., Brierley, J., McDougall, M., Carter, M., Tremoulet, A., Shimizu, C., Herberg, J., Burns, J. C., Lyall, H., & Levin, M. (2020). Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. *JAMA - Journal of the American Medical Association*, *324*(3), 259–269. https://doi.org/10.1001/jama.2020.10369
17. World Health Organisation. (2020). *Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19: Scientific brief*. World Health Organization. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
18. Yuliarto, S., Susanto, W. P., Kadafi, K. T., Ratridewi, I., & Olivianto, E. (2021). Potential severe pediatric sars-cov-2-induced multisystem inflammatory syndrome resembles dengue infection. *Tropical Biomedicine*, *38*(2), 129–133. https://doi.org/10.47665/TB.38.2.048