EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.20081

Original Article

Multiorgan dysfunction syndrome in sepsis: Is macrophage activation syndrome secondary to infection?

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Abstract

Objective: To assess macrophage activation syndrome (MAS) in septic shock leading to multiorgan dysfunction syndrome (MODS).

Methods: A prospective observational study was conducted at a tertiary care hospital to evaluate the MAS criteria in different stages of sepsis. Children aged 6 months to 12 years in different stages of septic shock were recruited. The Paediatric Rheumatology International Trials Organisation Collaborative Initiative (PRINTO) criteria of MAS were applied initially at the stage of septic shock and subsequently at the stage of MODS (MODS cohort) or following recovery from septic shock without going through MODS (non-MODS cohort).

Results: A total of 127 subjects were studied, with 53 comprising the MODS cohort and the rest 74 the non-MODS cohort. At the initial assessment, a comparable proportion of subjects in the MODS and non-MODS groups satisfied the MAS criteria (20.75% and 25.68%, respectively; p=0.529). However, by the time of progression to MODS, 81.13% of the subjects satisfied the MAS criteria in the MODS group, whereas only 16.18% subjects in the non-MODS group continued to satisfy the MAS criteria (p<0.001). Thus, there was a definite increase in the proportion of subjects showing MAS by the time they progressed to multiorgan dysfunction (p<0.001). In contrast, the proportion declined significantly (25.68% to 16.18%; p=0.008) in the subjects who had recovered.

Conclusion: The findings bear out the hypothesis that MODS in sepsis is a reflection of MAS secondary to sepsis. However, studies in larger cohorts are needed to validate these findings and explore the therapeutic implications.

Keywords: Sepsis syndrome, macrophage activation syndrome, multiorgan dysfunction syndrome, immune response

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Cite this article as: Nandy A, Mondal T, Sarkar M, Nag SS, Chel S, Ivan DM, et al. Multiorgan dysfunction syndrome in sepsis: Is macrophage activation syndrome secondary to infection?. Eur J Rheumatol 2021; 8(2): 89-92.

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Submitted: May 09, 2020
Accepted: September 08, 2020
Available Online Date: November 19, 2020

Introduction

Rapid progression of illness without florid manifestation is a frequently observed phenomenon following sepsis in children. Awareness of this phenomenon is important because the management should be tailored according to the course of illness (1). Among several determinants, immune response has been identified as one of the principal factors likely to be involved in modulating the outcome of sepsis. The development of sepsis-induced multiple organ dysfunction (MODS) is presumed to be a sequel to multiple cytokine mediated aberrant immunological response elicited at an earlier stage of the illness (2). Familiarity with the macrophage activation syndrome (MAS), which can be observed as a manifestation of aberrant immunological response in different autoimmune diseases, has led to the hypothesis that sepsis-induced MODS is a similar phenomenon triggered by abnormal immunological expression (3). If the 2 are analogous phenomena, then the identification of MAS using relatively simple criteria that do not involve sophisticated laboratory testing may be of immense benefit in resource constrained settings. This could point to the possibility of MAS in MODS and allow the institution of timely therapeutic measures (3-5).

Aberrant host immune function in response to sepsis could have a detrimental effect by inducing the development of MODS (6). A catastrophic proinflammatory phenomenon has often been proposed to be associated with sepsis even when the culprit pathogen could not be isolated (7). Therefore, if MODS is perceived as a final common pathway for dysregulated immune response in sepsis, and if the proinflammatory dysregulated immune response can be identified and managed appropriately at the incipient phase, the

outcome should be better in terms of reduced mortality. Such a proinflammatory response of the body has been documented in different names such as MODS by the intensivists, MAS by the rheumatologists, and hemophagocytic lympho-histiocytosis by the oncologists (2, 3, 8). Leaving aside these semantic controversies, the abnormal immune response can be viewed as the hidden link between all these conditions and can be analyzed for effective treatment modalities.

Methods

We conducted a prospective observational study in a tertiary care teaching hospital during 2018-2019. Ethics committee approval was received for this study from the North Bengal Medical College, Darjeeling, India (Approval Date: February 01, 2019; Approval Number: IEC/NBMC/2018-19/91). Children between 6 months and 12 years of age, admitted with or developing septic shock after admission, were recruited as study subjects. Written informed consent was obtained from the parents. Subjects with known comorbid conditions like autoimmune illnesses, hemoglobinopathies, previous blood transfusions, or chronic diseases, and those patients who had received corticosteroids or any immunomodulator therapy were excluded.

The children were studied along the course of their illness, initially at the stage of septic shock and then again either at the stage of recovery or the stage of MODS. Relevant medical records including the clinical examination and laboratory reports were reviewed. Core body temperature of ≥100.4ºF recorded by rectal thermometer was considered as fever in the subjects. To satisfy the laboratory components, the following cut-off values laid down in the original MAS criteria (5) were followed: platelet count $<1.81\times10^3$/mL, serum ferritin >684 ng/dL, serum aspartate transaminase (AST) >48 Units/L, serum triglyceride >156 mg/dL, and serum fibrinogen level <360 mg/dL. A criterion was considered to be present if the value was above or below the applicable cut-off.

The Paediatric Rheumatology International Trials Organisation Collaborative Initiative (PRINTO) diagnostic criteria for MAS were applied at the stage of septic shock and subsequently at the stage of MODS after progression of the illness. Similar evaluation was also conducted in the remaining subjects who recovered from the septic shock without going into MODS and remained hemodynamically stable for at least 1 week. Each of the 6 components of the MAS criteria, including fever and serum ferritin level, was assigned with a score 0 or 2 for absence or presence, respectively. A total score of ≥6 out of 12 was taken as the cut-off value for the state of illness to qualify as MAS.

Statistical analysis

Data were compiled into a Microsoft Excel spreadsheet and analyzed by Statistica version 6 (StatSoft Inc; Tulsa, Oklahoma, USA) and MedCalc version 15.8 computer software (MedCalc Software Ltd; Mariakerke, Belgium). Independent proportions were compared by Fisher's exact probability test and paired proportions by McNemar's chi-squared test. The 2-tailed p value of <0.05 was considered statistically significant. Diagnostic indices (sensitivity, specificity, positive predictive value, negative positive predictive value, likelihood ratio positive, and likelihood ratio negative) of each individual MAS criterion were calculated along with their 95% confidence intervals.

Results

A total of 138 children in septic shock were identified as potential study subjects, of whom 127 were recruited after exercising the inclusion and exclusion criteria. Among them, 53 subjects deteriorated to the stage of MODS, whereas 68 recovered from stage of septic shock, and 6 of them died in the stage of septic shock without progressing to MODS. Despite the best efforts of the intensive care support, 11 (20.75%) subjects who progressed to MODS succumbed to their illness. Subjects who did not develop MODS from the stage of septic shock and those progressing to MODS along

Main Points

- Aberrant immunological response is likely in the course of sepsis and possibly leads to multiorgan dysfunction.
- The composite MAS criterion has a better prospect in identifying MAS in MODS compared with individual components of MAS criteria in isolation.
- Serum ferritin had 100% sensitivity and negative predictive value, but the specificity was 33.3% in defining MAS in MODS.
- Sepsis-induced multiorgan dysfunction may be reflective of MAS being secondary to sepsis in a sizable number of patients.

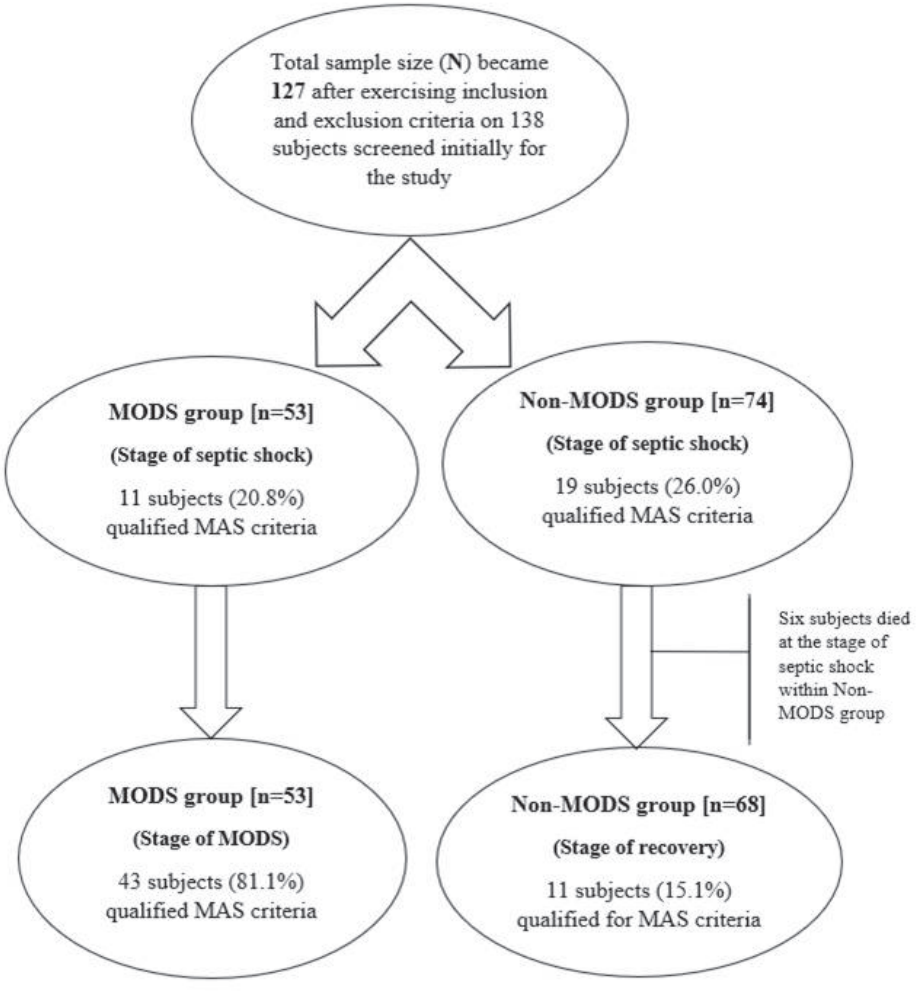

Figure 1. Flowchart depicting distribution of subjects with study progress.

Table 1. Comparison of proportions of subjects satisfying the MAS criteria during the course of their illness.

	MODS group	Non-MODS group*	p** (between group)
Stage of septic shock	11/53 (20.75%)	19/74 (25.68%)	0.529
Subsequent stage (MODS or recovery)	43/53 (81.13%)	11/68 (16.18%)	<0.001
p** (within group)	<0.001	0.008	

*In the non-MODS group, 6 children succumbed in the stage of septic shock without recovering.
**p values in the last column are from Fisher's exact test, whereas those in the last row are from McNemar's test.
MAS: macrophage activation syndrome; MODS: multiorgan dysfunction syndrome.

Table 2. Diagnostic performance indices of individual components of the MAS criteria for defining MAS in the MODS group.

	Sensitivity [%] (95% CI)	Specificity [%] (95% CI)	PPV [%] (95% CI)	NPV [%] (95% CI)	LR+	LR-
Fever (>100.4°F)	50.0 (33.4-66.6)	33.3 (7.5-70.1)	76.0 (54.9-90.6)	13.6 (2.9-34.9)	0.75	1.5
Platelet count (<181×10^3/µL)	65.8 (48.7-80.4)	77.8 (39.9-97.1)	92.5 (75.7-99.1)	35.0 (15.4-59.2)	2.9	0.4
Serum ferritin (>684 ng/dL)	100.0 (90.8-100.0)	33.3 (7.5-70.1)	86.4 (72.7-94.8)	100.0 (29.2-100.0)	1.5	0
Serum aspartate transaminase (>48 Units/L)	84.2 (68.8-93.9)	33.3 (7.5-70.1)	84.2 (68.8-93.9)	33.3 (7.5-70.1)	1.3	0.5
Serum triglyceride (>156 mg/dL)	50.0 (33.4-66.6)	77.8 (39.9-97.2)	90.5 (69.6-98.8)	26.9 (11.6-47.8)	2.3	0.6
Serum fibrinogen (<360 mg/dL)	68.4 (51.4-82.5)	77.8 (39.9-97.2)	92.9 (76.5-99.1)	36.8 (16.3-61.6)	3.1	0.4

LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; MAS: macrophage activation syndrome; MODS: multiorgan dysfunction syndrome; CI: confidence interval.

the course of illness were designated as non-MODS group (n=74) and MODS group (n=53), respectively. In the MODS group, the MAS criteria were applied at the stage of septic shock and the exercise repeated at the point when they developed MODS. In the non-MODS group, the criteria were applied initially in the stage of septic shock and after the child had recovered from septic shock and remained hemodynamically stable for at least 1 week. Figure 1 summarizes the categorization of study subjects along the course of illness.

Table 1 indicates the proportion of subjects satisfying the composite MAS criteria in the 2 study groups. At the initial assessment in the stage of septic shock, 20.75% and 25.68% of the subjects in the MODS and non-MODS groups satisfied the MAS criteria; this difference was not significant statistically (p=0.529). However, by the time of progression to MODS, 81.13% of the subjects satisfied the MAS criteria in the MODS group, whereas only 16.18% subjects in the non-MODS group continued to satisfy the MAS criteria (p<0.001). Thus, there was a definite increase in the proportion of subjects showing MAS by the time they progressed to multiorgan dysfunction (p<0.001). In contrast, the proportion declined significantly (25.68% to 16.18%; p=0.008) in the subjects who recovered. In fact, during the latter stage of the illness when evolution to MODS or recovery was evident, the relative risk of continuing to have MAS was 5.01 (95% confidence interval, 2.87-8.75) in the MODS group compared with its non-MODS counterpart.

Individual components of the MAS criteria were analyzed subsequently to look for their potential in capturing the MAS condition in the MODS group. The performances on various diagnostic indices have been depicted in Table 2. Overall, the impression was that the application of the composite MAS criteria had a better prospect compared with individual components in isolation when they were considered for a given situation. Serum ferritin had 100% sensitivity and negative predictive value, but the specificity was unacceptably low at 33.3%.

Discussion

The dysregulation of the host immune response in sepsis has been observed to be an important variable in determining the sepsis outcome. In view of macrophage activation like syndrome in sepsis as stated by Kyriazopoulou et al. (7), an immune response which led to cytokine mediated proinflammatory phenomenon impressed the researchers (4). However, this has been a subject of debate when a blunted immune response was witnessed in sepsis (7). Considering both situations, it was understood that either immune paralysis or excessive immune activation causing a cytokine storm could influence the course of the illness after sepsis occurred. In certain instances, sepsis-induced MODS was inferred as a hyper-ferritinemic sepsis related phenomenon with an abnormal immune activation (3, 4).

The challenge for practitioners is to identify such abnormal immunological response with authority. This study provides an insight to the aforementioned missing link. MAS has been an established manifestation of abnormal immunological function in different rheumatologic diseases, and assessment of this condition could indirectly provide information regarding the contemporaneous abnormal immunological expression in sepsis (3, 9). Accordingly, we attempted to determine whether the MAS criteria could be used to identify the underlying inappropriate immunological expression leading to sepsis-induced MODS. To the best of our knowledge, there were no such prospective controlled studies in children available in the literature.

In our study, although in the initial stage of septic shock, there were relatively few subjects categorizable as experiencing MAS, a significant proportion of subjects who developed sepsis-induced MODS went on to fulfil the MAS criteria. However, the initial proportion fell significantly among subjects who recovered from septic shock without going into the stage of MODS. This observation raises the question, with a certain degree of conviction, of whether it is the MAS that is leading to sepsis-induced MODS. Sepsis could have acted as an inciting factor for the aberrant immunological response which ultimately manifested as different organ dysfunctions in MODS (10). In our study, we mostly observed no growth of pathogenic organisms in sepsis-induced MODS, yet the progressive derangement of different organ functions was unmistakable. It can be inferred that sepsis-induced MODS might simply be the end result of the MAS related cytokine storm.

Focusing on the individual criteria in the MAS portfolio, it was observed that the serum fer-

ritin level had the highest sensitivity, whereas serum fibrinogen level had the maximum likelihood ratio to determine MAS condition in sepsis-induced MODS. However, individually none of these criteria had an acceptable balance of the various diagnostic indices to qualify as a single factor assessment for MAS. Thus, it is more reliable to consider a composite criterion for declaring MAS as originally proposed till a modified MAS score applicable for sepsis becomes available.

Our study has its share of limitations. Although we have dealt with the concern of excessive immune activation in childhood sepsis, it is worth noting that we have not explored whether deaths occurred because of immune paralysis. A study of immunological markers in a larger cohort of septic shock cases is needed to address this dilemma. Measurement of individual cytokines, natural killer cell dynamics, and other indicators, which we could not do because of logistical limitations, would have given us direct evidence to discern a cytokine storm in bacterial sepsis. The MAS criteria represent an accepted tool for identifying aberrant and excessive immunological response underlying the cytokine storm in autoimmune diseases. We have used that in an analogous manner in the context of sepsis. More studies are needed to validate this analogy.

In the context of the recent pandemic of coronavirus disease 2019 (COVID-19), similar observations have been made, and the mortality of cases has been related to MODS. Comorbid illnesses have been identified as important risk factors for aggravating organ dysfunction. Again, we may see proinflammatory MAS-like phenomenon triggered by immune dysregulation being identified as a forerunner for the development of MODS in these patients. It is worth noting that various groups around the world have proposed the use of immunomodulators in severe cases (11, 12). A lot more research is needed, but it seems like the COVID-19 morbidity and mortality could be related to immune dysfunction mediated proinflammatory cytokine storm and arresting this dysregulated immune cascade may be a worthwhile approach in saving seriously ill patients.

In conclusion, we can say that our study bears out the hypothesis that MODS in sepsis is a reflection of MAS being secondary to sepsis. However, studies in larger cohorts are needed to validate these findings and explore the therapeutic implications.

Ethics Committee Approval: Ethics committee approval was received for this study from the North Bengal Medical College, Darjeeling, India (Approval Date: February 01, 2019; Approval Number: IEC/NBMC/2018-19/91).

Informed Consent: Informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.M.; Design - R.M., A.N., S.S.N.; Supervision - R.M., M.S., A.H.; Materials - A.N., S.S.N.; Data Collection and/or Processing - A.N., S.S.N., D.M.I., S.C.; Analysis and/or Interpretation - T.M., S.C., A.H.; Literature Search - D.M.I., T.M., S.C.; Writing Manuscript - D.M.I., M.S., A.N.; Critical Review - R.M., T.M., M.S., A.H.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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