PERSPECTIVE

Is Severe Dengue a Cytokine Storm Syndrome?

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ABSTRACT

The immunopathogenesis of dengue severity remains an enigma. There is a growing body of evidence pointing towards a transient hyperinflammatory hypercytokinemic state responsible for the development of severe dengue including dengue hemorrhagic fever that coincides with the onset of thrombocytopenia, capillary leak, multiorgan dysfunction and hyperferritinemia. There are several reports of dengue associated hemophagocytic lymphohistiocytosis (HLH). However, the cytokine storm in dengue as well as in other infections may not conform to the classic HLH 2004 diagnostic criteria. Following the recent COVID-19 pandemic, there has been a paradigm shift in the understanding of infection-associated cytokine storms. There is a need to explore timely short-course immunotherapy for the management of selected patients with dengue spiraling into the critical phase.

Keywords: *Dengue severity, Hypercytokinemia, Hemophagocytic lymphohistiocytosis*

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INTRODUCTION

Dengue continues to be a menace not only in India but also in the majority of South East Asian countries. Two vaccines have recently been licensed but are yet to be approved in India [1]. Fluid therapy still remains the mainstay of management of dengue. Although 80 to 85% patients have an uneventful clinical course, the remaining require hospitalization and a few of these progress to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which are associated with a significant mortality. There is growing evidence that an underlying cytokine storm plays a major role in the pathophysiology and is responsible for the subsequent multiorgan dysfunction.

Hypercytokinemia is a hyperinflammatory state which includes related but not identical conditions such as cytokine release syndrome (CRS), cytokine storm syndrome (CSS), primary and secondary hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Hypercytokinemia occurs due to hyperactivation of cytokines and other proinflammatory markers which can be triggered by infectious pathogens, malignancies, autoimmune and autoinflammatory states.

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Though the HLH 2004 criteria are frequently used for the diagnosis of infection-induced hyperinflammation/ hypercytokinemia, these are mostly a forceful extrapolation and lack sensitivity and specificity [2].

Hypercytokinemic states can have myriad clinical manifestations often leading to shock, vascular leak and disseminated intravascular coagulation. It can sometimes present as overt HLH or MAS. Laboratory manifestations may include cytopenia, deranged liver and kidney function and raised inflammatory markers like C-reactive protein (CRP), serum ferritin, serum triglyceride and serum lactate dehydrogenase (LDH).

In the recent COVID-19 pandemic, around 20% patients progressing to severe disease resulting from hypercytokinemia, were managed with corticosteroids and other immunomodulatory drugs [3]. A meta-analysis noted that in the RECOVERY trial, use of dexamethasone was associated with a significant reduction of deaths in severe COVID-19 [4]. Another hypercytokinemic state emerged during this period called the multisystem inflammatory syndrome in children (MIS-C) where corticosteroids and intravenous immunoglobulin were useful therapeutic strategies [5]. This raises the issue of analogy with other infectious conditions with tumultuous course.

Transient Hypercytokinemic Phase of Dengue

Dengue fever is characterised by a febrile phase usually lasting 5 to 7 days characterised by high fever, headache, muscle and joint pain, loss of appetite and rash. Defervescence of fever may be followed by a critical

phase in 5 to 10% patients who manifest with features of plasma leakage and hemorrhage which constitutes severe dengue. The exact pathophysiology leading to severe dengue is still unknown. Several studies have noted that both the innate and the adaptive immune systems are activated which contribute to increased cytokine production. The transient period of vascular leak followed by rapid recovery seems to suggest the effects of short-lived biochemical mediators, such as interleukins (IL-1, IL-6, IL-8, IL-10, IL-18), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and interferon-gamma (IFN-γ) [6-9]. Both pro-inflammatory and anti-inflammatory cytokines have been shown to play a role in the pathogenesis of dengue, an understanding of which can aid therapeutic decisions. While elevated levels of pro-inflammatory cytokines like IL-6, IL-8, and TNF-α, may promote inflammation and aid clearance of dengue virus, anti-inflammatory cytokines like IL-10 and TGF-β may lead to immunosuppression, poor antiviral response and an uncontrolled inflammatory reaction, which may contribute to the development of severe dengue.

Secondary dengue infections have been known to be clinically more severe and these correlate with excess cytokine production due to the antibody-dependent enhancement (ADE) effect. This is related to the antibodies from previous infection being unable to neutralise the current heterologous antigen, which thereby easily accesses the Fc presenting cells leading to persistent immune stimulation. However, there is a paucity of data on clinical findings and simple bedside tests which can help in the early identification of the cytokine storm [8].

Dengue and HLH

Several studies have shown HLH as a known complication of dengue fever. A large study from Southern India comprising of 212 dengue patients identified 31 (14.6%) patients who developed HLH including 23 with bone marrow evidence of hemophagocytosis [10]. Another study from Kolkata reported 2.2% children with HLH during the 2012 dengue outbreak. These children presented with prolonged fever, cytopenia, organomegaly, negative culture and showed good response to dexamethasone [11]. A case series of 33 children with HLH from Chennai, Tamil Nadu, had 5 dengue cases [12].

Hyperferritinemia, a hallmark of hyperinflammatory states and HLH, has been noted in severe dengue. A study from Malaysia on 180 adult patients with severe dengue had high ferritin as one of the factors directly corelating with mortality. They suggested prompt HLH-directed therapy in severe dengue patients with hyperinflammation and evolving multiorgan failure [8].

Severe Dengue: Cytokine Storm Syndrome vs HLH Conundrum

Considering that the HLH 2004 protocol is predominantly designed for the diagnosis of familial and genetic HLH, it may not be completely applicable for diagnosing other secondary HLH including those associated with rheumatological diseases, infections and malignancies [13]. These are diverse entities and the same diagnostic criteria will not be applicable for all. Ravelli et al had published separate criteria to diagnose MAS in 2016 which are applicable to MAS in systemic onset juvenile idiopathic arthritis. In contrast, infection-associated hyperinflammatory states are far more heterogenous where the HLH criteria may not be applicable and it would possibly be better to label them as cytokine storm syndromes, cytokine release syndromes, or, in the absence of cytokine levels in routine clinical practice, simply as hyperinflammatory states [14]. The recent COVID-19 pandemic is a remarkable example of such an infection-associated hyperinflammatory state where the HLH protocol was not used for diagnosis, and treatment with anti-inflammatory drugs like dexamethasone, IL-6 antagonist tocilizumab, or Janus kinase (JAK) inhibitor baricitinib were used based on laboratory markers of

Box I Defining Dengue Cytokine Storm Syndrome

Patients developing thrombocytopenia (platelet count $\leq 100 \times 10^3/mm^3$) and rising PCV (elevation of 10% over baseline) i.e., those going into the leaky phase will be further tested for hyperinflammation.

Hyperinflammation will be defined as:

- Serum ferritin > 500 ng/mL
- CRP < 12.5 mg /L (normal 5 mg/L): to exclude associated sepsis

AND atleast 3 of the following:

- Elevated lactate dehydrogenase (≥ 280 U/L)
- Fasting triglyceride (≥ 265 mg/dL)
- Serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) > 3 times upper limit of normal
- Low sodium (< 130 meq/L)
- Low albumin (< 3.5 g/dL)

Table I Studies on Therapeutic Strategies for Dengue Related Hemophagocytic Lymphohistiocytosis/ Hyperinflammation

Study group	*Study design*	*Study population*	*Intervention*	*Outcome*
Intervention: Steroids (Methyl prednisolone or dexamethasone)				
Premaratna et al [18]	Retrospective	23 patients with hypotensive Dengue Shock Syndrome (DSS) in febrile phase were given steroids (group A) and retrospectively compared with 32 comparable patients who did not receive steroids (group B)	Intravenous (IV) methylprednisolone 1g, single dose	3/23 in group A succumbed vs 15/32 in group B; Group B required significantly more intensive care treatment and fluids than group A. Mean time to hemodynamic stability in group A was 5.8 h vs 18.2 h in group B
Pal et al [11]	Retrospective	Out of 358 dengue patients, 8 developed HLH who received intervention	IV dexamethasone at 10 mg/m^2 in 3-4 divided doses till hemodynamically stable, then shifted to oral route in a tapering dose for 21 days, additional IVIG was given in one child	In 7 children, fever subsided within 48-72 hours of starting steroids, cytopenia resolved over next 4-7 days, serum ferritin normalised within a week
Jasmine et al [23]	Descriptive, case series	A case series of four patients	All four received IV methylprednisolone	All four were successfully discharged
Tam et al [24]	Randomized controlled trial	225; the treatment group received oral steroids early during the acute phase of dengue (patients with dengue and fever for ≤ 72 hours) with the aim to assess potential harm from steroid use during viraemic phase	75 each in placebo, high dose prednisolone 2 mg/kg, low dose prednisolone 0.5 mg/kg	All patients recovered fully; Placebo: 22 had any adverse events, 10 had serious adverse event, 5 had dengue shock, 1 had significant bleeding, 10 had increased liver enzymes. Low dose steroid group: 16 had any adverse events, 6 had serious adverse event, 5 had dengue shock, 3 had significant bleeding, 7 had increased liver enzymes. High dose steroid group: 23 had any adverse events, 14 had serious adverse event, 8 had dengue shock, 1 had significant bleeding, 6 had increased liver enzymes. Possible drug related adverse events (no in each low dose, high dose, placebo): Hyper-

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Study group	*Study design*	*Study population*	*Intervention*	*Outcome*
				glycemia (5,7,3), hypertension (0,0,1), pneumonia (1,0,1) upper respiratory tract infection (2,2,1) Use of oral prednisolone for 3 days in early phase was not associated with significant clinical or virological adverse effects. Subsequent development of recognised complications such as DSS, significant bleeding, thrombocytopenia, coagulopathy was similar across the three groups. With DSS as end point relative risk for high dose prednisolone vs placebo was 1.62 ie. high dose steroids may reduce the risk of shock by 43%.The study was not powered to study efficacy.
Intervention: Intravenous immunoglobulin				
Raju et al [10]	Not mentioned	Out of 212 dengue patients, 23 children had HLH	19 received IVIG, 4 did not receive anything	All 19 who received IVIG recovered. 3 of remaining 4 died of complications.
Others				
Ramachandra et al [12]	A retrospective analysis	43 were diagnosed as HLH, 33 fulfilled the criteria of HLH 2004. 3 had EBV, 5 had dengue, 1 had CMV and bacterial etiology was seen in 5.	22 received corticosteroids (IV methyl prednisolone or dexamethasone) 21 received IVIG 11 unresponsive patients also received cyclosporine, 5 received etoposide	Improvement of blood parameters noted in 5-7 days. 25 (76%) were successfully discharged. Dengue HLH data not separately available.
Tan et al [25]	Case report	A case series of 6 patients with dengue HLH	4 received pulse methyl prednisolone,1 received additional IVIG	Out of the 5 who received immunotherapy, 4 were successfully discharged and 1 succumbed. The lone patient who did not receive immunotherapy was also succesully discharged.

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Study group	*Study design*	*Study population*	*Intervention*	*Outcome*
Wan Jamaludin et al [26]	Case report	3 cases of dengue HLH	Dexamethasone plus IVIG	All successfully discharged
Meta-analysis				
Giang et al [27]	Meta-analysis	45 articles, 122 patients	Not mentioned	Pooled fatality for dengue associated HLH was 14.6%
Intervention not mentioned				
Ellis et al [28]	Retrospective	22 identified as dengue HLH	The study was on incidence and risk factors for developing dengue associated HLH, therapeutic intervention not mentioned in the study	1 died

inflammation like raised CRP [5].

The success of treating a hyperinflammatory state is dependent on the timely identification and intervention, before the initiation of a vicious cycle of cascading inflammation and multiorgan dysfunction. Early administration of anti-inflammatory medications in the course of infection to all patients maybe deleterious considering an ongoing viremic phase and that only 10 to 15% of dengue patients will go into the critical phase. Again, intervention in an established dengue shock maybe too late and ineffective. Most studies in dengue suggest the onset of critical phase is heralded by vascular leak and associated hyperferritinemia. This is the point where short-lived biochemical mediators seem to take over the pathophysiological milieu and dictate the future clinical progression of the disease [7]. In majority of dengue patients this leaky phase typically coincides with the onset of afebrile phase and hence the classic HLH criteria may not be applicable.

Dengue and Immunotherapy

There is limited and sometimes conflicting evidence on the use of immunomodulation in dengue fever. Since the last century there have been few publications on the use of corticosteroids in dengue with variable outcomes [15,16]. A Cochrane systemic review included eight randomized controlled trials (RCTs) or quasi randomised studies, and stated that the evidence of steroid efficacy in dengue was very low and insufficient to conclude its benefit when given at an early stage or in DSS [16]. The timing of steroid administration and patient selection are critical for a successful outcome, and administering steroids too early or too late in the disease course may lead to lack of benefit [17].

Some reports have demonstrated the successful use of dexamethasone in dengue-associated HLH. A retrospective study in adults with dengue and very severe disease found that giving single dose 1g intravenous methylprednisolone as rescue therapy in DSS resulted in lesser mortality (3/13 patients) than not giving (15/32 patients) [18]. The Ana Den is an ongoing clinical trial in Vietnam on the possible effects of Anakinra in dengue patients with hyperinflammation as compared to placebo [19]. There are some reports on the successful use of Anakinra in dengue-associated hyperinflammation including one from India where it was used in steroid-IVIg resistant dengue HLH [20].

The first step for managing dengue CSS would be arriving at acceptable clinical criteria for defining the same. Criteria suggested for defining dengue-associated hyperinflammation are outlined in **Box I**. **Table I** summarises the published studies on dengue HLH/ hyperinflammation along with the respective interventions and outcomes. Several of these strategies seem promising. Further studies can help arrive at evidence-based recommendations for managing CSS.

CONCLUSIONS

Dengue associated hyperinflammation is an increasingly recognized, but under diagnosed entity, and the mortality in those with hyperinflammation remains almost twice (39%) than in those without (22%). Although the National Guidelines for the Management of Dengue Fever mention cytokine storm and vasculopathy in pathogenesis of severe dengue, it fails to mention ways of riding the storm [21]. Unfortunately, attempts at evaluation of immunotherapy in severe dengue have not progressed [22]. There is a need to draw attention of the authorities, academicians and industry to focus on this neglected domain [22]. Considering the disease burden and its effect on public health every year, the need of the hour is to recognize the hyperinflammatory phase of dengue and address it in time. There might be a role of immunomodulation in DSS/CSS,

however prospective RCTs are needed to define the exact therapy.

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