Pediatric Adenovirus-Associated Hemophagocytosis Lymphohistiocytosis - A Single Centre Experience From Eastern India

Under the broad umbrella term cytokine storm syndrome, a constellation of illnesses characterised by uncontrolled immune activation leading to hyperinflammation and multiorgan disease due to excessive cytokine release, are recognized. Though adenovirus is said to be a relatively common cause of secondary hemophagocytic lympho-histiocytosis HLH [1], pediatric literature is infrequent and limited to case reports and small series [2]. Herein, we report our experience with 15 cases of adenovirus HLH during the recent outbreak in eastern India.

This retrospective study was conducted in the pediatric department of a tertiary care centre. The records of children aged 1 month to 16 years, proven to have adenoviral infection via nasopharyngeal swab testing between January to April 2023 were reviewed (*n* =106). Fifteen patients (10 boys, 5 girls) who fulfilled criteria for H score positivity (> 169) with a sensitivity of 93% and specificity of 86%, and also received treatment for the same were included, data collected and tabulated (**Table I**). Out of 15 children, 12 were walk-ins, three children were referred patients. The mean age of patients was 1.8 (1.24) years, ranging from 3 months to 53 months. Four children presented in the first week, six in the second week and remaining five in the third week of illness. All children had fever and cough. Breathlessness was present in five children (33%) at presentation. Seven children (46%) had gastrointestinal along with respiratory symptoms. Reactive HLH was suspected due to persistence of fever beyond first week, organomegaly and cytopenias. Once appropriate cultures were negative and H score was calculated to be > 169, the diagnosis of HLH was committed and treatment started. The mean (SD) H score was 227.3 (18.9) with an accuracy of 96-98%. None of the children underwent a bone marrow examination for demonstrating hemophagocytosis, implying that H score with high predictability may be present in majority of patients without a need for invasive procedures. The mean (SD) ferritin was 12705.7 (12476.2) ng/mL in all children; the mean ferritin in survivors was 11291 ng/mL and 18364.3 ng/mL in non-survivors. Most children who developed HLH had severe adenovirus pneumonia (93%); 8 children needed respiratory support with non-invasive ventilation or high flow nasal canula or central positive airway pressure assistance, and six needed mechanical ventilation due to respiratory failure. Transaminitis was present in all patients, with seven children (46%) fulfilling Pediatric Acute Liver Failure (PALF) criteria [3]. Three patients with ALF had bleeding manifestations (upper GI) needing blood products. Two had acute kidney Injury (AKI), with one child needing peritoneal dialysis. All children were initially started on dexamethasone monotherapy, and if no clinical and laboratory response was noted in 48 hours, treatment escalated to Intravenous Immunoglobulin (IVIg) or pulse steroids or both. Eight (53%) children responded to steroids only protocol (Dexamethasone, starting @ 10 mg/m^2/day, duration titrated to response). The mean (SD) duration of pediatric intensive care unit stay was 7.7 (2.2) days. Three children expired and 12 survived.

The adenovirus outbreak in eastern India from December 2022 onwards was attributed to recombinant adenovirus type B 7/3 as per non-peer reviewed reports [4]. Adenoviral infections are known to be associated with innate immune overactivation and NK cell dysfunction [5]. It is interesting to note that HLH was noted in 14% (15/106) of children admitted with adenovirus infection in our institution during this outbreak. Our data may have a bias as only the more sick cases may have been referred to our tertiary care centre. Additionally, we used H score to detect adenovirus infection which is a more sensitive criterion but our observation makes a case for adenovirus-associated HLH being more common than previously reported and needs further study.

Severe adenovirus pneumonia is commonly present in patients who go on to develop HLH as seen in our series. (14/15, 93%) The role of liver injury in this regard cannot be underestimated, with transaminitis present in 100% of cases. Liver was the most common target organ noted with liver failure in up to 46%. It may be postulated that local organ damage in lung and liver may be driving the inflammatory response which when uncontrolled leads to cytokine storm. HLH in all children occurred in the second week of illness, as reported in earlier studies [6]. This provides a window of opportunity for early detection and diagnosis.

While the HLH 2004 criteria may have better validation for familial HLH [7], the H score based on less

Table I Clinical, Laboratory Characteristics, Treatment Received and Outcome Data of all Patients

Parameter	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
Age (Months)	27	10	47	6	24	16	6	36	16	3	36	7	27	36	53
H score	250	239	224	219	180	239	214	214	219	254	206	229	234	239	250
Ferritin (ng/mL)	21000	14500	5921	6425	3124	12404	2715	2520	28172	50618	12369	2570	2600	12400	13248
Respiratory support NIV (HFNC / CPAP)	N	N	Y	N	N	Y	Y	Y	N	Y	Y	Y	N	Y	N
Mechanical ventilation	Y	Y	N	Y	N	N	N	N	Y	N	N	N	Y	N	Y
Inotropic support	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
Hepatic encephalopathy	N	Y	Y	Y	N	Y	N	N	Y	N	N	N	N	N	Y
Acute kidney injury	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N
Hospital acquired infection	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N
IVIg	Y	N	N	N	N	Y	N	N	Y	Y	Y	Y	N	N	N
Pulse steroids	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N
Length of PICU stay (d)	12	13	6	5	-	6	7	7	7	9	6	7	8	7	9
Mortality	Y	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N

AKI Acute Kidney Injury; CPAP Continuous Positive Airway Pressure; HFNC High Flow Nasal Cannula; NIV Non-Invasive Ventilation; IVIg Intravenous Immunoglobulin; PICU Pediatric Intensive Care Unit; N No; Y Yes

rigorous criteria is being validated, more recently, for secondary HLH [8,9]. It is interesting to note that demonstration of hemophagocytosis is not compulsory for the diagnosis of HLH. The usage of more sensitive H score with a reasonable specificity has important clinical implications as it may be useful for early recognition and treatment. Treatment for secondary, infection-induced HLH is not standardised but milder protocols including steroids only or steroids and intravenous immunoglobulin (IVIg) have been reported with good results, including in adenovirus-associated HLH [2]. Reported survival rate for secondary HLH varies between 55-76% [10]. In our small cohort, survival was 80 %.

In conclusion, it is important to have a high index of suspicion for reactive HLH in any pediatric patient with continued fever beyond the first week with cytopenias and organomegaly.

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