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Case Report

Hemophagocytic Lymphohistiocytosis in a patient with Dengue Hemorrhagic Fever

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Abstract

HLH is an uncommon, fatal complication of dengue infection and often leads to multi-system involvement and failure. Early recognition and prompt initiation of appropriate immunosuppressive therapy is crucial in improving the outcome. We report a case who developed secondary HLH following dengue haemorrhagic fever. An 8 year and 5-month-old child who was managed as dengue haemorrhagic fever, had persistent fever, hepatosplenomegaly, bicytopenia, hyper-ferritinemia (> 20000), and hypertriglyceridemia. He was diagnosed with HLH according to the diagnosis criteria. This child was treated with steroids and supportive care following which the child made a gradual recovery. Second-line immunosuppressive treatment was not required in this case. Once sepsis is excluded, HLH should always be suspected early in this type of patient. Early appropriate immunosuppressive treatment is important to improve the long term outcome and prevent mortality.

Keywords: *Hemophagocytic Lymphohistiocytosis, Dengue Hemorrhagic Fever*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages[1]. It is estimated that approximately 1 child in 3000 admitted to a tertiary care pediatric hospital will have HLH[2].

HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases[1].

Familial HLH usually follows an autosomal recessive inheritance. About 40 to 60 percent of the mutations occur in PRF 1 and Unc-13 Homolog D (UNC13D) genes. Other genes involved are Syntaxin 11 (STX 11) and Syntaxin Binding Protein 2 (STXBP2) [3, 4]

Secondary HLH is usually acquired by malignant or non-malignant (infectious, non-infectious, and iatrogenic) conditions. Epstein-Barr virus (EBV) is the most common agent to cause HLH, which has poor outcomes [5]. Currently, there is increasing data that implies that severe dengue virus infection also causes secondary HLH with poor outcomes. The mortality may increase up to 43% [6].

Dengue-associated HLH has been well-reported in children, however, only a few case reports have been identified in adults. Out of the four dengue viruses, DENV1, DENV3, and DENV4 have been identified to cause HLH. Due to the increasing number of dengue detections every year, dengue-associated HLH has increased as well[10].

As per HLH-2004 diagnostic criteria, HLH is diagnosed when at least five of the eight criteria listed are fulfilled. These criteria are fever, splenomegaly, cytopenia affecting at least two of three lineages in peripheral blood, ferritin ≥500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer (NK) cell activity, and high level of soluble interleukin-2 receptor alpha chain (CD25) [11]

Prompt treatment is critical, but the greatest barrier to a successful outcome is often a delay in diagnosis due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings [10].

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Pediatricians must consider HLH in dengue-infected patients if they observe persistent fever, abnormal mental state, cytopenia with organ issues, and, importantly, ferritin greater than 10,000 μg/L. Due to its anti-inflammatory effect, pulse doses of glucocorticoids (methylprednisolone or dexamethasone) can be used in the treatment of dengue-associated HLH. Intravenous immunoglobulin G can be used either alone or with dexamethasone or methylprednisolone. The dengue-associated HLH diagnosis is challenging but it is very important to recognize it as it is associated with better treatment options [12].

Case Presentation

An 8-year-old and 10-month-old boy was admitted to the ward with a history of high-grade continuous fever for 3 days duration, nausea, and a few episodes of vomiting associated with right hypochondrial pain. He also had frontal headache, myalgia, dizziness, and anorexia without any respiratory or urinary symptoms. The headache was not associated with photophobia or phonophobia. He passed urine just before the admission. He was ill-looking, the capillary refilling time was less than 2 sec and he was not pale or icteric. There was no lymphadenopathy. His pulse rate was 124/min while his blood pressure was 110/60 mmHg and had warm peripheries. There was tender hepatomegaly on abdominal examination. Other respiratory and neurological examinations were unremarkable.

Full blood count on admission WBC - 4.40 x 10^9/L(N-78.2%, L-17.5%), Hb- 13.8 g/dL, PLT- 203 x 10^9/L, AST - 71 (U/L), ALT -37 (U/L), Na - 133 mmol/L, K - 4.4 mmol/L (Table 1).

Febrile phase monitoring initiated. Input and output chart maintained. Supportive care was given. Antiemetic drugs and paracetamol started.

The following day (Day 4) - Fever and right hypochondrial pain persisted, and a few episodes of vomiting and loose stools developed. On examination: Had tachycardia and tender hepatomegaly. WBC and PLT dropped (Table 1), PCV raised, and USS findings revealed free fluid in the Hepatorenal pouch. Critical phase monitoring started. The next day WBC and PLT counts further dropped, LFT worsened (Table 1), PCV rose. Critical phase monitoring was continued. Fluid therapy and IV cefotaxime along with IV paracetamol were given as well as GCS was monitored.

Day 6 and Day 7 of illness- In addition to continuous high spike fever developed fluid overload symptoms and worsening of increased sleepiness and irritability. On examination: facial puffiness and periorbital oedema were noticed. He had tachycardia, tachypnea, R/S pleural effusion, ascites and the GCS was 14/15. AST and ALT are highly raised (Table 1). Troponin- negative. Fluid restriction was done, IV NAC, IV Vitamin K regular dose, IV omeprazole and rifaxamine were added.

Day 8 of illness – HLH was suspected as there was no improvement. S.ferritin>20000 ng/L (Table 2), Fibrinogen level - 2.6 g/L, Fasting triglyceride level 3.3 mmol/l (292 mg/dl), AST-4242 (U/L), ALT- 947(U/L), CRP- 10.7 mg/L, ESR- 32 mm/1st hr , LDH 4981 U/L. Blood picture: anemia suggestive of intercurrent illness and mild to moderate thrombocytopenia, CXR- mild pleural effusion .USS - Mild splenomegaly with B/L Mild pleural effusion and Ascites.

The child was managed withIV methylprednisolone 30 mg/kg given for 5 days preceding pulse therapy of oral dexamethasone 10 mg/m^2. Follow-up serum ferritin level (Table 2) done while monitoring the clinical outcome. Day 12 child recovered and discharged home.

Table 1 : Summary of Basic Blood Investigations

Investigation	Day 3	Day4	Day5	Day 6	Day 7	Day 8
WBC (x 10^9/L)	4.40	3.98	5.59	10.32	10.15	9.75
Neutrophils (x 10^9/L)	3.44	3.24	3.38	4.89	4.90	5.62
PLT (x 10^9/L)	203	94	22	16	49	102
Hb (g/dL)	13.8	14.4	14.8	14.7	12.4	11.9
AST (U/L)	71	353	399	613	3248	4652
ALT (U/L)	31	66	95	145	842	3190

Table 2 : Summary of Serum Ferritin Levels

Day	Serum Ferritin (ng/L)
Day 8	>20000
Day 9	7160
Day 11	5060
Day 12	2600

Discussion

HLH is an uncommon, potentially Life threatening hyper inflammatory and hemophagocytic syndrome which causes severe hypercytokinemia with excessive activation of lymphocytes and macrophages. It is associated with various conditions [15].This case report describes a patient who developed HLH following dengue haemorrhagic fever. Acquired HLH can occur in a patient with dengue and is a rare manifestation. The diagnosis of HLH may be challenging in dengue due to overlap of the clinical features [15].

The diagnosis of HLH was made based on features like increased serum ferritin and triglyceride level according to HLH protocol [4]. Compared to other cases bone marrow biopsy was not done as invasive investigations like bone marrow biopsy was not required to diagnose HLH in this case [14,15].

The management principles of HLH include suppression of hyperinflammation, elimination of activated immune cells, elimination of triggers, supportive therapy, and replacement of defective immune systems [14]. Treatment protocol contains induction, salvage, and continuation therapy [4].

Suppression of hyperinflammation and elimination of activated immune cells can be achieved with corticosteroids, intravenous immunoglobulin, cyclosporine, anti-cytokine agents like etoposide, and monoclonal antibodies [15]. Corticosteroids are the first choice to suppress the hypercytokinemia [14].

In this case, the child was managed with intravenous methylprednisolone for 3 days followed by oral dexamethasone induction along with supportive management for the critical phase of dengue and liver involvement. After the acute management follow-up was arranged for this patient with a plan of tailing off dexamethasone over 8 weeks. This patient had an excellent response to treatment with steroids alone like other similar cases reported [15].

A favorable outcome was able to be achieved in this case due to early recognition and initiation of treatment like few other HLH cases reported [14,15].

Conclusion

Dengue-associated HLH is a rare but potentially life-threatening condition. It is associated with severe dengue fever such as dengue haemorrhagic fever or dengue shock syndrome [12]. Persistent fever following dengue infection may point towards sepsis or expanded dengue syndrome including HLH [12]. Early recognition and prompt initiation of appropriate immunosuppressive therapy are crucial for reducing morbidity and mortality [13].

Consent

Written informed consent was taken from the parents for the publication of the case.

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