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Hemophagocytic Lymphohistiocytosis (HLH): An Unusual Presentation of Dengue Fever in Children

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Abstract

Dengue is a common but potentially deadly illness, which can be complicated by hemophagocytic lymphohistiocytosis (HLH). This report describes two cases of dengue fever in otherwise healthy individuals who faced challenges due to HLH. The diagnosis was established by meeting the clinical and laboratory criteria for HLH. Both patients were successfully treated with a pulse regimen of methylprednisolone and other supportive measures. This case report highlights the importance of early diagnosis and appropriate treatment for HLH patients to reduce morbidity and mortality associated with this condition.

Key words: dengue fever, hemophagocytic lymphohistocytosis

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Introduction

Dengue fever (DF) is a viral disease transmitted by Aedes mosquitoes, primarily found in tropical and subtropical countries.[1] It is also commonly seen in Bangladesh. Most cases of dengue fever can be managed at home. However, morbidity and mortality rates can be high when DF presents with plasma leakage. In addition to the typical symptoms, dengue fever can also manifest in atypical ways, such as intracranial hemorrhage, facial palsy, encephalitis, reversible blindness, and acute motor quadriparesis.[2] In 2011, the World Health Organization (WHO) introduced the concept of Expanded Dengue Syndrome (EDS) to address the wide range of unusual presentations associated with this common disease, which may involve the liver, kidneys, heart, brain, or bone marrow[3]. Increasing evidence suggests that a significant cytokine storm plays a crucial role in the pathophysiology of dengue fever and is a key factor in the resulting multi-organ dysfunction[4].

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Hemophagocytic lymphohistiocytosis (HLH) is a severe medical condition that can be life-threatening. It is characterized by excessive inflammation caused by the uncontrolled proliferation of activated lymphocytes and histiocytes, which release significant amounts of inflammatory cytokines[5]. HLH is classified into two types: primary (genetic) and secondary (acquired). The secondary form is often triggered by viral infections, autoimmune disorders, or neoplastic diseases[6]. The dengue virus is increasingly recognized as a major cause of secondary hemophagocytic lymphohistiocytosis (HLH). Severe cases of dengue infection pose a high risk of mortality, with death rates for individuals developing secondary HLH reaching up to 43%[7]. Treatment for severe dengue complicated by HLH may require the use of systemic corticosteroids, intravenous immunoglobulin, or chemotherapy[8]. In this report, we present two cases of dengue-related HLH that resulted in favorable outcomes, thanks to timely diagnosis and intervention.

Case 1:

A 4-year- 8-month-old boy, 1st issue of non-consanguineous parents hailing from Dhaka, with no prior medical illness, presented with fever for 16 days, which was high grade continued in nature: he also developed abdominal pain. On examination he was febrile, irritable and hepatosplenomegaly was found. With all these complaints he was initially diagnosed as a case of dengue fever (Dengue NS_1 positive) and was getting treatment in a tertiary care hospital. As the fever

was persisting and also developed scrotal swelling, he was referred to Bangladesh Medical University (BMU) for further evaluation and management. Upon arrival to BMU he was hemodynamically stable but irritable and febrile along with ascites and scrotal swelling. His initial investigation showed pancytopenia, SGPT was raised with low serum albumin. Blood culture and urine culture were normal. Patient was initially managed with crystalloid and colloidal fluids. The patient remained febrile on day 18, and further investigations revealed that biochemical markers (Serum Ferritin, Triglycerides, SGOT, LDH, SGPT) were significantly elevated. Echocardiography and bone marrow study were normal. Finally, the patient was diagnosed as Dengue Fever with HLH and treated with an injection Methylprednisolone (25mg/kg/day) for consecutive 3 days followed by oral prednisone for the next 4 weeks with tapering mode. Patient was declared cured during follow-up.

Case 2:

A 9-month-old female child presented with dengue fever (NS_1 positive) and got admited in a tertiary care hospital in Dhaka and treated accordingly. During her hospital stay she developed convulsion and was shifted to PICU (Pediatric Intensive Care Unit).. In the meantime, she was afebrile having generalized oedema with tachycardia and unstable BP also developed hapatosplenomegaly. Lab reports showed cytopenias, abnormal SGPT, high ferritin level, high triglyceride with low albumin and fibrinogen. Bone marrow study could not be done as patient was not vitally stable. Bone marrow study could not be done as patient was vitally unstable. After proper clinical and laboratory evaluation patient was diagnoses as DF with HLH. After proper clinical and laboratory evaluation patient was considered as DF with HLH. She received I/V fluids, injectable antibiotics, injection methylprednisolone, anticonvulsant and dopamine. The challenging issue was patient developed refractory shock in spite of getting adequate ionotropes. After receiving the injection Methyleprednisolone for 3 days this patient was vitally stable and then we switched to oral prednisolone for another 4 weeks. After one month of hospital stay patient was improved and was discharged with advice.

Table I

Lab parameters of both the cases before and after treatment of HLH

Lab tests	Before treatment case 1	Before treatment case 2	After treatment case 1	After treatment case 2
Haemoglobin	8.1 gm/dL	9 gm/dL	11.5 gm/dL	12 gm/dL
Total count	3100/cumm	12000/cumm	5500/cumm	6500/cumm
Platelet	90000/cumm	125000/cumm	250000/cumm	250000/cumm
Ferritin	8745	537	750	137
SGPT	255 U/L	1261 U/L	40 U/L	38 U/L
LDH	594 U/L	600 U/L	289 U/L	250 U/L
Triglyceride	666 mg/dl	557 gm/L	190 mg/dl	150 gm/L
Albumin	2.6 gm/L	2.4 gm/L	4.7 gm/L	4.1gm/L
Fibrinogen	1 gm/L	1.2 gm/L	2 gm/L	2.5 gm/L

Discussion

Dengue virus is responsible for dengue infection and comprises four distinct serotypes, with serotypes 2 and 3 associated with higher mortality rates.[7] The fundamental pathological mechanisms involve plasma leakage and haemorrhage, which may progress to shock and death. In cases of severe dengue, extensive T-cell activation and an increase in proinflammatory cytokines contribute to adverse outcomes.[9] Patients with severe dengue have a greater risk of developing secondary hemophagocytic lymphohistiocytosis (HLH), a condition that can further increase mortality rates.[7]

HLH is a hyperinflammatory disorder marked by the activation of macrophages, which engage in the phagocytosis of blood cells within the bone marrow. This process triggers a cytokine storm, resulting in organ dysfunction and potentially leading to death.[10,11] Viral infections are a common trigger of HLH. Acquired HLH can affect children of any age.[12] For establishing HLH, at least five criteria should be fulfilled out of the eight listed below. These include (1) fever, (2) splenomegaly, (3) cytopenia affecting at least 2 of 3 lineages in peripheral blood, (4) ferritin 500 ìg/L, (5) hypertriglyceridemia and/or hypofibrinogenemia, (6) hemophagocytosis in bone marrow or spleen or lymph nodes, (7) low or absent NK cell activity, and (8) high level of soluble CD25. A highly elevated serum ferritin level is strongly related to HLH.[13]

Our patient, case 1 had features of dengue fever including fever, headache, body ache, abdominal discomfort. NS1 antigen and dengue IgM positive verified the diagnosis, enabling continued treatment. Fever that continues after a dengue infection may be due to sepsis and expanded dengue syndrome (HLH). So, further workup ruled out sepsis. Patient had fever, splenomegaly, cytopenia, high ferritin level, hypertriglycedemia who fulfilled five out of eight HLH 2004 diagnostic criteria. Unfortunately, bone marrow report was normal. It is important to mention that the sensitivity and specificity of hemophagocytosis for HLH are 83% and 60%, respectively. Consequently, a negative initial bone marrow sample should not postpone the diagnosis and start of HLH therapy.[14] Clinical manifestations of our case was similar to other case reported by Momin from India.[15]

In case 2 patient had dengue fever (NS1 positive), convulsion with refractory shock. In this case patient was afebrile but vitals were unstable after 10 days of treatment. Refractory shock, splenomegaly, cytopenia, high ferritin, hypofibrinogenemis, abnormal SGPT were in favor of HLH.

Kay Choong See on his review article recommended to treat dengue associated with HLH patients with I/V methyleprednisolone followed by oral prednisole.[16] Our patients were treated with I/V methyleprednisole for three consecutive days followed by oral prednisolone. Case 1 responded well with resolution of fever and improving blood parameters. Case 2 also responded with recovered from shock and blood parameters became normal. Similar to our report there are many reports showed favorable outcome of Dengue associated with HLH while treating with steroids1.[4,16,17] Corticosteroids are frequently used as the first line of treatment; however, etoposide, intravenous immunoglobulin, and intrathecal Methotrexate can be second option of treatment of HLH[18]. Although it is becoming more widely acknowledged, dengue-associated hyperinflammation is still underdiagnosed, and the mortality rate for those who have it is still nearly double (39%) as opposed to those who didn't (22%). Ways to ride the storm are not mentioned in the National Guidelines for the Management of Dengue Fever, despite the fact that they discuss cytokine storm and vasculopathy as part of the pathophysiology of severe dengue.[19] Further studies can help arrive at evidence-based recommendations for managing these complicated cases.

Conclusion

HLH is a rare but serious complication that can arise from dengue infection. Healthcare professionals should be particularly vigilant for signs of HLH in patients diagnosed with dengue, especially if they have a persistent fever lasting more than seven days, show any signs of cytopenias, or have significantly elevated serum ferritin levels. Early recognition of this condition and prompt treatment with corticosteroids are essential for improving clinical outcomes.

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