

# Severe dengue with acute fulminant hepatitis and secondary hemophagocytic lymphohistiocytosis: A case report

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## Abstract

**Background:** In dengue virus infection, high levels of viremia is associated with involvement of multiple organs (liver, brain) in the severe form of the disease. The liver is the commonest organ to be involved in dengue.

**Case report:** We describe a case of severe dengue in 1 year old female child which was complicated by acute fulminant hepatitis (AFH), secondary hemophagocytic lymphohistiocytosis (HLH), encephalopathy and respiratory failure. Severe dengue was managed according to dengue protocol with ventilator support. N – acetylcystine infusion was given for acute fulminant hepatitis. Liver functions and encephalopathy improved with N – acetylcystine infusion. HLH was diagnosed according to the diagnostic criteria of the histiocyte society and intravenous immunoglobulin (IV Ig) was given as treatment. Child improved with IV Ig and was discharged.

**Key words:** Severe dengue, Acute fulminant hepatitis, Hemophagocytic Lymphohistiocytosis.

## Introduction

Dengue fever caused by dengue virus (DENV), has 4 serotypes (DEN 1-4) and is a member of the flaviviridae family and the genus Flavivirus. With DENV infection, high level of viremia is associated with involvement of multiple organs (liver, brain) in the severe form of the disease<sup>[1]</sup>.

The liver is the commonest organ to be involved in dengue. Hepatic involvement is either due to direct viral effector dysregulated immunologic injury in response to the virus. Elevation of transaminase levels can occur as part of dengue, after resuscitation from shock (ischemic hepatitis) or in the form of acute fulminant hepatitis (AFH)<sup>[2,3]</sup>.

Hemophagocytic syndrome is an aggressive disease characterized by excessive immune activation. It can occur in the setting of autoimmune disease, hematological malignancy and infections. Infection by dengue virus is being recognized as a cause of secondary hemophagocytic lymphohistiocytosis (HLH) in the recent years<sup>[2,4]</sup>.

We describe a case of severe dengue in 1 year old

female child which was complicated by acute fulminant hepatitis and secondary hemophagocytic lymphohistiocytosis.

## Case report

A 1 year old female child born to non-consanguineous marriage came to emergency ward with complains of fever for 3 days, cough, hurried breathing and abdominal distension for 1 day. She was completely immunized till date with normal developmental milestones.

On examination there was grade I PEM (IAP) with mild pallor (Hb 9.8gm/dl), respiratory distress (Respiratory rate-80/min), abdominal distension and tender hepatomegaly (span - 8cm). Child had features of compensated shock. Child had positive dengue NS1Ag antigen and severe thrombocytopenia (15000 cells/cumm) with elevated liver enzymes (SGPT –800IU/L) on admission day 1 (Table 1). USG showed gross ascites with bilateral mild to moderate pleural effusion with minimal pericardial effusion (Figure 1).

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**Figure 1. Bilateral pleural effusion with pericardial effusion**

Treatment was given according to dengue protocols, shock got corrected but platelets dropped further (7000 cells/cumm) and child developed GI bleed (malena) on day 2. Single donor platelets and packed red blood cells were transfused. Child developed hepatic encephalopathy with further elevation of liver enzymes (SGPT- 2940 U/L and TSB 4.0 mg %) on 4<sup>th</sup> and 5<sup>th</sup> day of admission (Table 1). Child was ventilated on day 7 for 4 days in view of poor sensorium (encephalopathy) and respiratory failure. Child was started on N-acetyl cysteine infusion for acute liver failure and elevated liver enzymes according to Lim G et al<sup>[5]</sup>. Sensorium improved over next few days with improvement in liver functions. In view of fever spike, persistent thrombocytopenia, elevated ferritin, triglycerides and hepato-splenomegaly, child was presumptively diagnosed as secondary HLH.

**Table 1. Trend of the various hematologic parameters**

	Day 1	Day2	Day 4	Day 5	Day 6	Day 8	Day11	Day13	Day16	Day17
HB (g/dl)	9.4	13.5		9.1	13.9	11.5	12.7	10.1	10.3	11.8
WBC (cells/mm <sup>3</sup> )	5900	6000		6700	12300	12100	8200	3200	6200	8600
HCT	26.6	37.7	28.0	25.9	38.1	30.0		28.7	30.2	34.0
Platelets (cells/mm <sup>3</sup> )	15000	7000	10000	35000	16000	7000	5000	3000	30000	90000
SGPT (IU/L)	800	-	1060	2970	2410	1460	400	-	314	-
SGOT (IU/L)					3230					
TSB (mg/dl)	-	-	4.0	-	2.4	-	-	-	-	-
PT/APT	-	-	-	-	18.3/55	16.4/64.9	-	-	-	-
INR	-	-	-	-	1.4	1.2	-	-	-	-
Triglycerides (mg/dl)							118	202		90
Sr.ferritin (ng/dl)							1132	1394		140

Bone marrow aspiration showed hemophagocytosis which confirmed the diagnosis of HLH. Intravenous immunoglobulin (IV Ig) was given to treat HLH and platelets improved over few days of treatment. During the recovery, serum ferritin and triglyceride levels improved back to normal levels after IV Ig therapy.

## Discussion

The incidence of dengue virus infections in infancy is 5-20%. Management of infants with severe dengue is challenging because early diagnosis is difficult as many of them present with unusual manifestations and complication such as hepatic dysfunction and fluid overload and also the case fatality rate is higher. In dengue infection, mild elevation of transaminases (<5x) is a common finding. Elevation more than 10 times is rarely reported<sup>[6,7]</sup>.

In India and Thailand, dengue infection is the most important cause of acute hepatic failure in children contributing to 18.5% and 34.3% of the cases respectively<sup>[8]</sup>. These unusual clinical forms of hepatic disease are frequently associated with more serious states, and they often result from multifactorial conditions, such as the use of hepatotoxic drugs, in addition to the direct aggression by the dengue virus<sup>[6]</sup>.

Hemophagocytic lymphohistocytosis (HLH) does not feature in the World Health Organization's guidelines on dengue, either in the disease classification or in the complications. However, during the past two decades, HLH has been reported occasionally as a complication of dengue<sup>[2,3]</sup>. Pro-inflammatory cytokines play an important role in the pathogenesis of dengue infection as well as HLH, thus forming the pathogenetic link

between the two<sup>[9]</sup>. Laboratory features of secondary HLH include cytopenias; deranged liver function tests, coagulopathies; raised serum ferritin; lactate dehydrogenase and triglycerides; and bone marrow hemophagocytosis. Diagnosis of HLH is based on the diagnostic criteria of the Histiocyte Society<sup>[10]</sup>. Our patient fulfilled the criteria on the basis of having fever, cytopenia, raised ferritin, triglycerides and hepato-splenomegaly and bone marrow findings of HLH. Effective initial therapy consists of a combination of pro-apoptotic chemotherapy and immune-suppressants which target activated macrophages/histiocytes (etoposide, steroids, high-dose IV IgG)<sup>[4]</sup>.

### Conclusion:

- Paediatrician should be aware of atypical dengue manifestations of dengue fever in children
- Secondary hemophagocytic syndrome should be kept in mind when dengue has unusual course.
- Usage of hepatotoxic drugs like anti-pyretic and anti-emetics during the early phase may initiate or potentiate the liver damage.

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