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Original Research Paper

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HEMOPHAGOCYTOSIS: AN UNUSUAL COMPLICATION OF CLASSICAL DENGUE FEVER WITH ACUTE LIVER FAILURE.

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ABSTRACT Dengue is a vector-borne disease caused by dengue virus. It has a diverse presentation and usually presents as an asymptomatic, self-limiting disease. Among the unusual presentations, hepatic dysfunction is well reported. Complications of dengue fever can be protean and life-threatening. Dengue may cause bone marrow suppression leading to thrombocytopenia, leukopenia and anemia in acute phase of illness; and increased hematocrit due to capillary leakage, but these changes are self-limiting and require no further investigations and specific treatment. Dengue associated Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of Dengue haemorrhagic fever or Dengue shock syndrome. Diagnosis of secondary HLH (sHLH) due to dengue is usually challenging and delayed as initial clinical symptoms mimic sepsis and systemic inflammatory response syndrome (SIRS). Delayed or no treatment of sHLH has a poor outcome. We present an unusual case of classical dengue fever presented as Acute liver failure (ALF) with encephalopathy, later complicated by sHLH.

KEYWORDS : Hemophagocytic lymphohistiocytosis (HLH), secondary HLH (sHLH), Acute liver failure (ALF), Dengue Fever (DF).

INTRODUCTION:

Dengue causes a wide spectrum of disease ranging from asymptomatic subclinical infection to multiorgan dysfunction leading to death. It has unusual presentation like myositis, encephalitis, hepatitis. [1,2] Liver involvement in dengue is varied with mild to moderate elevation in liver enzyme to rarely, fulminant hepatic failure presenting as ALF. [3]

HLH is characterized by over activation of the immune system. As a result of this, there occurs phagocytosis of mature blood cells and their precursor within reticuloendothelial cells by macrophages.

Classical DF presenting as ALF with hepatic encephalopathy, complicated by HLH is seldom reported. Here we report a case of a three-year-old child presented as ALF with stage 1 hepatic encephalopathy diagnosed as DF on day 9 of illness. The case was later complicated by HLH secondary to DF.

Case Report:

A three-year-old, developmentally normal female child, with no significant past history presented to the emergency room with high-grade fever for 5 days, yellowish discoloration of the sclera and abdominal distention since 2 days. On inquiry the child had altered sleep pattern, increasing day time sleepiness and irritability since 2 days. The child had no history of myalgia, headache, rashes over body, vomiting, abdominal pain, hematemesis, malena, hepatotoxic drug intake, toxin ingestion or blood transfusion in past. On physical examination the child was well built, height-96 cm (between the median and +1SD), weight-15kgs (between the median and +1 SD), HR- 118/min, RR-30/min, BP-98/42mmHg, SpO2- 95% on room air. The child had icterus, pedal odema. On superficial abdominal palpation, there was mild hepatic tenderness, no guarding and rigidity. Deep abdominal palpation revealed hepatomegaly of 9cm below costal margin with soft consistency, smooth surface and rounded border with liver span of 14.5 cm. The spleen was palpable 9 cm below left costal margin along the long axis of the spleen. The child was irritable, conscious, oriented to time place and person, sensory and motor system examination normal, no focal neurological deficit or signs of meningeal irritation. Other system examination was unremarkable.

The patient's investigations revealed deranged Liver function test and coagulopathy as depicted in table1. Chest roentgenogram was normal. Ultrasonography of the abdomen showed hepatosplenomegaly with minimal nontappable ascites.

Table 1 laboratory parameters from day 5 of illness

	Reference value	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 14	Day 21
Hb	11.3/14.2g/dL	13.4	11.2	10.8	8.4	8.0	7.6	7.0	9.2
Hct	33-41%	42	35	30	25	24.3	22	20	28
WBC	5500-15500	8236	6234	3958	4320	3812	3618	4140	7880
Platelet	150000-450000	192678	111450	82000	70240	52400	58210	38000	96000
T bili	<1.2mg/dL	6.4	4.3			3.4		3.8	1.0
D bili	<0.2 mg/dL	2.1	1.2			1.1		1.2	0.2
ALT	5-45U/L	598	449			326		378	66
AST	13-35U/L	824	734			690		448	88
ALP	100-320U/L	984	624			464		492	312
Albumin	3.4-5.4gm/L	3.6	3.2			2.4		1.7	4.7
BUN	5-18mg/dL	14	18			12		16	14
Sr creat	0.3-0.7mg/dL	0.4	0.5			0.3		0.4	0.4
Na	133-145mEq/L	136	133			140		134	135
K	3-5.6mEq/L	4.4	4.0			3.2		3.0	4.4
PT	11-13.5 sec	20	14			12			
Aptt	30-40 sec	82.3	52			34			
INR	0.8-1.2	2.1	1.3			0.8			
RBS	60-100mg/dL	104	122						
Ammonia	30-70mcg/dL	134							
LDH	110-295U/L					842		976	

(Hb-haemoglobin, Hct- haematocrit, T bili-Total bilirubin, D bili- Direct bilirubin, ALT-Alanine transaminases, AST-Aspartate transaminases, ALP- Alkaline phosphatase, Sr

creat-serum creatinine, Na-sodium, K-Potassium, BUN- blood urea nitrogen, PT- prothrombin time, aPTT- activated partial thromboplastin time, INR-international normalized ratio, RBS-Random blood sugar, LDH- lactate dehydrogenase).

The child presented in ALF with stage 1 hepatic encephalopathy, was started on hepatic drip (100ml normal saline with 400ml 10% dextrose, 5ml potassium chloride and calcium gluconate, 2ml multivitamin injection), injection Vitamin K, Fresh Frozen Plasma (FFP) intravenous N acetylcysteine (NAC), syrup lactulose, and Intravenous cefotaxime. NS1 antigen for dengue, serology (IgM) for dengue and leptospirosis was negative. Rapid malarial antigen test negative. IgG and IgM serology for viral hepatitis (A, B, C, E) were negative. EBV DNA PCR and CMV PCR were negative. Considering acute on chronic liver failure further workup for autoimmune hepatitis and Wilson's disease were done. The tests revealed no evidence of Coombs negative hemolytic anemia, normal serum ceruloplasmin, & 24 hr urinary copper and slit-lamp examination of the eyes thus ruling out Wilson's disease. Antineutrophilic antibody (ANA), Liver kidney microsome type 1 antibody (Anti LKM1), Anti Smith antibody tests were normal with normal serum IgG level, which ruled out autoimmune hepatitis. Blood culture and urine culture did not show any growth. On day 9 of illness child had persistent fever spike, hemogram was suggestive of leukopenia and thrombocytopenia. Repeat serology for dengue IgM was done which was positive which was confirmed by positive Dengue RTPCR. Serial blood count monitoring was suggestive of dropping trends of all three-blood cell lineage. The child had pancytopenia, persistent fever spike with hepatosplenomegaly hence further workup for HLH was done. It revealed raised serum ferritin 15732ng/ml (7-140 ng/ml), triglyceride 520mg/dl (27-125mg/dl), low fibrinogen 92mg/dl (150-350 mg/dl). Bone marrow biopsy showed hemophagocytes suggestive of HLH. As per diagnostic criteria for HLH 2004 our case fulfilled 6 out of 8 criteria of HLH. She was started on intravenous steroids (Dexamethasone -10 mg/m2) following the diagnosis.

DISCUSSION:

Dengue virus belongs to the Flaviviridae family and has 4 serotypes DEN1, DEN2, DEN3, DEN4. Hepatic dysfunction in dengue may present with mild to moderate elevation in hepatic transaminase to severe hepatic failure presenting as ALF. The pathogenesis of liver dysfunction in dengue infection is exactly not known. Various theories are postulated to explain this a) direct effect of the virus or host immune response on liver cell, b) splanchnic hypoperfusion leading to circulatory compromise and hypoxic injury due to plasma leak. [3] NAC infusion can be given for non-acetaminophen induced liver damage, as NAC scavenges free radicals formed due to hypoxic injury. Anti-inflammatory, antioxidant, inotropic and vasodilating property of NAC has a beneficial effect in treating non-acetaminophen induced hepatotoxicity. [4]

HLH may be primary (familial) and secondary (acquired). Primary HLH have a genetic basis, whereas secondary HLH is associated with infection, hematological malignancy (T cell lymphoma), autoimmune disease. [5] In half of the cases of etiological factor is infection. Among this in one-third of cases, the viral infection is triggering factor, EBV infection being the most common. [5]

Dengue associated HLH is commonly seen in a patient with dengue hemorrhagic fever or dengue shock syndrome, however, there are some reports of HLH in a patient with primary dengue fever. [6] T cells infected with dengue virus produce cytokines leading to uncontrolled histiocytic activity. [7] A various study done till now showed that three serotypes of dengue virus (DEN1, DEN3, DEN4) are associated with sHLH. [7] sHLH due to dengue usually present in the second week of illness HLH is diagnosed by histiocyte society criteria 2004. If five out of eight criteria are present it is confirmed as HLH—splenomegaly, bicytopenia, fever, hyperferritinemia, hypertriglyceridemia, hypofibrino genemia, hemophagocytes in tissue specimen and increase CD25/IL-2 receptor or reduced NK cell function. [8] Treatment policy for sHLH is mostly treatment of triggering infection. Some cases may require treatment with corticosteroids, in severe cases immunosuppressants like etoposide and cyclosporine are required. [8]

In our case child presented in ALF with encephalopathy as the presenting complaint which is a rare entity and was successfully managed. NAC and lactulose helped in early recovery. Serology (IgM) & PCR studies for dengue were positive on day 9 of illness. Persistent fever hepatosple nomegaly with pancytopenia setting in since day 9 of illness diagnosis of sHLH was made started on steroids. Our patient showed good response to steroid after 2 days of starting steroids in the form resolution of fever and normalization of CBC in a week. The child had favorable response in initial week of starting steroids hence other immunosuppressants (etoposide, cyclosporine) not required. Steroids were tapered over a period of 8 weeks. There were no signs of reactivation after completion of 8 weeks of steroid therapy.

CONCLUSION:

Hepatic dysfunction as a complication of dengue is commonly seen, ALF as a presenting complaint in dengue fever is rare and has a morbid profile, hence early suspicion and prompt management can give a better outcome. The febrile period in dengue fever lasts for a week, hematological parameters gets normalized till day 10th of illness; persistence of fever with hematological and liver enzyme derangement beyond clinical recovery should be taken as an alarming sign to evaluate further. Re-revising the diagnosis at regular interval should be practiced.

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