Original article

Hepatic profile and platelet count as a prognostic indicator in Dengue fever, from a tertiary care hospital in south India.

[1]Dr.Shashidhara Kuppegala Chikkaveeraiahm , [2]Dr.K.M.Srinath , [3Dr].Sumanth Kumar k, [4] Dr.Prabhath Kiran Reddy

[1]Asso.Prof of Medicine, J.S.S Medical College, JSS University, Ramanuja Road, Mysore, 570004, Karnataka.

[2] Asso.Prof Of Medicine, J.S.S Medical College, JSS University, Ramanuja Road, Mysore, 570004, Karnataka.

[3]Post graduate in General Medicine J.S.S Medical College, JSS University, Ramanuja Road, Mysore, 570004, Karnataka.

[4.] Post graduate in general medicine, J.S.S Medical College, JSS University, Ramanuja Road, Mysore, 570004, Karnataka.

Corresponding Author: Dr.Shashidhara Kuppegala Chikkaveeraiah

Abstract:

Aims*:* Hepatic dysfunction and thrombocytopenia was common in dengue infection and the degree of liver dysfunction and thrombocytopenia varies from mild injury with elevation of transaminases to severe injury with jaundice. This study was undertaken to assess the hepatic dysfunction and thrombocytopenia in dengue infection.

Settings and design*:* Data was collected and analyzed by using SPSS – version 18.Descriptive statistical measures like, percentage, mean, correlation and standard deviation were applied.All the statistical methods were carried out through the SPSS for windows (version 18.0).A p value <0.05 was considered as significant.Data was presented as tables and graphs as relevant.

Methods and material: 100 patients with serologically positive dengue fever aged above 18 years were studied for their hepatic functions and platelet count both clinically and biochemically after excluding malaria, enteric fever, scrub typhus and leptospirosis, Hepatitis B with relevant investigations.

Results*:* The spectrum of hepatic manifestations included hepatomegaly (23%), jaundice (33%), raised levels of Aspartate transaminase (AST) (84%), Alanine transaminase (ALT) (84%), and abnormal abdomen ultrasound (33%) and Thrombocytopenia was seen in 98% of patients.

Conclusion*:* patients with fever, jaundice and tender hepatomegaly in geographical areas where dengue is endemic, the diagnosis of dengue fever with hepatitis should be strongly considered.

We observed bleeding diathesis is common in dengue fever with Hepatitis as compared to dengue fever without hepatitis.

Key-words: Dengue fever, DHF, DSS, AST, ALT.

Introduction:

Dengue is the most widely distributed mosquito-borne viral infection of humans, affecting up to 100 million persons each year across the tropical world.[1, 2] Infection with any of the four dengue viral serotypes may result in asymptomatic infection or may cause a range of disease manifestations from non-specific fever to a syndrome characterized by increased vascular permeability, thrombocytopenia, and deranged hemostasis. In severe cases, the increased vascular permeability results in circulatory compromise and the patient may develop potentially life-threatening dengue shock syndrome (DSS).[2– 4] No specific antiviral therapy is available but the

524

physiologic derangements are transient, and most patients recover fully if supported with parenteral fluid therapy during the period of maximal vascular leakage. Current mortality rates for DSS are less than 1% in experienced hands.[5-6]

The pathogenesis of Thrombocytopenia in dengue fever (DF) is not clearly understood. Increased peripheral destruction of antibody coated platelets is strongly suspected as the possible mechanism. Other modes include acute bone marrow suppression leading to a megakaryocytic condition and enhanced platelet destruction by the reticuloendothelial system [7,8]

Thrombocytopenia is a constant manifestation in dengue fever which often leads to life threatening dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). Both hemorrhagic diathesis and circulatory collapse are the fatal complications of dengue infection[9,10].

Thrombocytopenia and bleeding tendencies are the common problems in dengue which causes concern for the patients and treating doctors[2].Acute liver failure (ALF) associated with dengue fever has been described, with most reports occurring among children and a few individual case reports in adults[11]. In the studies involving children, fatal outcomes and a mortality rate of 50% had been reported[12]. The pathogenesis of dengue associated liver injury is not fully understood but Thought to be due to a direct viral effect or from a dysregulated immune response. Histological findings of hepatocytes necrosis at zone two and councilman bodies had been reported[13].

Other potential causes of hepatitis in dengue patients are ischaemic or hypoxic liver injury due to circulatory compromise and also drug induced liver injury since medications like acetaminophen or herbal remedies are usually taken for the commonly associated symptoms of fever and body aches. The aim of this study was to describe in details the clinical characteristics and outcome of a series of adult dengue patients with acute liver failure, a hepatology emergency which is no longer restricted to the tropics due to the increasing travel and trade.

Hepatic dysfunction is a well recognized feature of dengue infections, often demonstrated by hepatomegaly and mild-to moderate increases in transaminase levels although jaundice and acute liver failure are generally uncommon[14-17]. Debate continues as to whether dengue associated hepatic dysfunction indicates a direct viral effect, arises secondary to an aggressive host immune response to the virus, or reflects a complex interaction of these two mechanisms. The incidence of hepatic dysfunction is more in Dengue shock syndrome (DSS) and Dengue hemorrhagic fever (DHF) [17, 18, 13]. Aminotransferase levels are useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding [12, 18]. Hence early recognition and prompt initiation of appropriate supportive treatment can decrease the morbidity and mortality. Most of the data reported on abnormal liver functions in dengue are retrospective[17, 22, 24, 25]. Therefore we conducted a study on clinical features, thrombocytopenia, hepatic dysfunction and bleeding manifestations in 100 dengue patients. Objectives of the study are *to evaluate the clinical features, guesstimate the array of hepatic involvement and thrombocytopenia in dengue fever with respect to the prognosis and mortality in patients.* In recent studies from India and Thailand, dengue infection was the most important cause of acute hepatic failure in children contributing to 18.5% and 34.3% of the cases respectively[21, 22].

Subject and Methods:

The study was carried out in the medical wards of

JSS Medical college hospital, Mysore from October 2013 to October 2015. During this study period, all clinically suspected patients of dengue fever in individuals aged above 18 years of age were assessed and a detailed history and a thorough clinical examination were done and 100 patients who are either NS1 or IgM positive or both were included in the study. The diseases which resembles dengue fever like scrub typhus, leptospirosis, CMV, Influenza, was excluded by thorough clinical examination and relevant investigations if required. Under aseptic precautions single serum sample was collected from all clinically suspected dengue fever patients and was screened for following investigations, complete haemogram, LFT, RBS, Urea, Creatinine and dengue NS1 antigen and IgM anti dengue antibody by ICT, HBsAg, .For each sample included in this study, the information on hospital medical record number, laboratory identification number, age, gender, clinical findings, complete haemogram, LFT, chest x-ray findings and USG abdomen findings, dengue NS1 antigen, IgM anti dengue was recorded in a structured questionnaire and subsequently entered into **Microsoft excel software.** The necessary ethical clearance was obtained by the institutional ethics committee, J.S.S. Medical College, Mysore.

Statistical analysis used: Data collected was entered in to MS Excel 2010 – and analyzed by using SPSS – version 18.Descriptive statistical measures like, percentage, mean, correlation and standard deviation were applied.All the statistical methods were carried out through the SPSS for windows (version 18.0).A p value <0.05 was considered as significant.Data was presented as tables and graphs as relevant.

Results:

In the present study 100 patients with dengue fever formed the study subjects. Symptoms and signs of patients with dengue fever had been collected and liver function tests and platelet counts were done. Mean age of the total 100 patients was 34.8 years ranging from 18 to 60 years of age group. Majority of patients were in the age group of 21-30 years which constituted 33% of the total patients. There were 53 males and 47 females. Out of 100 patients with strong suspicion of dengue fever, 36 were dengue NS1 positive and 25 were dengue IgM positive and 39 were both dengue NS1 and IgM positive. Among 100 positive dengue patients either by dengue NS1 or by dengue IgM 18 patients were diagnosed to be dengue haemorrhagic fever and remaining 82 patients were diagnosed to be dengue fever.

Among 100 patients the most common symptom present was Fever, seen in all 100 patients followed by myalgia, headache and vomiting which were seen in 92 %, 83 %, 69 % respectively. Joint pains, retro orbital pain, diarrhoea were seen in 67%, 59%, and 9% respectively. Haemorrhagic manifestations in the form of gum bleeding or epistaxis or malena were seen in 18 % of patients. Cervical lymphadenopathy and icterus were observed in 46 % and 26 % of patients respectively (Graph1). The mean pulse rate observed was 87 beats per minute, 9 patients had bradycardia on admission and 25 patients had tachycardia on admission. The mean systolic blood pressure observed was121 mm of Hg. The mean diastolic blood pressure observed was 78 mm of Hg. 23 patients had hypotension on admission or during the hospital stay. Bilateral Pleural effusion was seen in all patients (23 %) and among them minimal ascites was seen in 7 patients. Oedematous gall bladder was seen in 15 % patients. The haemoglobin and PCV was normal in most of the patients with mean haemoglobin and PCV being observed was

526

13.39 mg/dl and 39.70 % respectively. In 15 patients there was raised haemoglobin above 16 mg/dl and PCVabove 45 %. Leucopenia was seen in 42 % patients and lymphocytosis was seen in 10% patients (Table1).

Thrombocytopenia was the most common laboratory finding present in all 100 patients. Mean platelet count at admission seen was77, 860 /cumm with minimum of 6,000/ cumm and maximum was 3, 33,000/cumm. Mean platelet count at discharge seen was 1,32,700/cumm with minimum of 23,000/cumm and maximum of 3, 40,000/cumm. Mean least platelet count seen during the hospital stay was 43,883/cumm with minimum of 1000/cumm and maximum of 2, 56,000/cumm. Lower the platelet count the chances of bleeding manifestations had increased (Table 2). Among 18 patients who had bleeding manifestations severe thrombocytopenia (platelet count<20,000) was seen in 13 patients and in remaining 4 patients it is in between 20,000 to 40,000 and in one patient it is in between 50,000 to 60,000.Severe thrombocytopenia is seen in 21 patients and among these patients 13 patients had bleeding manifestations.

In 84 % patients there is an increase in both aspartate and alanine aminotransferase. Mean total bilirubin seen was1.58 mg/dl with minimum of 0.2 mg/dl and maximum of 8.9mg/dl. Mean AST was 203 U/L with minimum of 33 U/L and maximum of 2880U/L. Mean ALT was 122 U/Lwith minimum of 19 U/L and maximum of 1250 U/L (Table3).

Among 18 patients who had bleeding manifestations total bilirubin is normal in 12 patients and in 6 patients it is in between 1mg/dl to 4 mg/dl. In these patients AST is increased in all patients, in 5 patients it is above 200 U/L and in remaining 13 patients it is in between 60 U/L to 200 U/L. In these patients ALT is normal in 2 patients and in other 2 patients it is more than 200 U/L and in remaining 14 patients it is in between 30 to 200 U/L .Among 32 patients who had total bilirubin of above 1 mg/dl bleeding manifestations is seen in 6 patients and remaining 26 patients doesn't have any bleeding manifestations. Among 84 patients who had increased AST, 18 patients had bleeding manifestations.
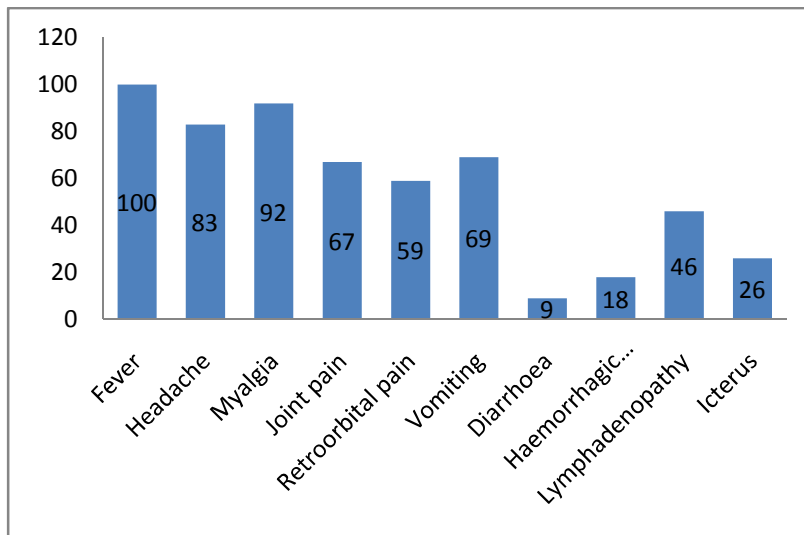
GRAPH 1: SYMPTOMS AND SIGNS

TABLE 1: Distribution of Haemoglobin, PCV, Total leukocyte count, urea and creatinine

	Mean	Minimum	Maximum
HB	13.39	6.50	21.60
PCV	39.70	20.40	60.30
TLC	5320.09	1340.00	16220.00
RBS	135.01	57.00	450.00
UREA	33.53	15.00	189.00
CREATININE	1.12	.70	7.90
ESR	29.04	5.00	110.00

TABLE 2: DISTRIBUTION OF PLATELET COUNT

	Mean	SD	Median	Minimum	Maximum
Platelet count at admission	77860.00	58647.90	62500.00	6000.00	333000.00
Platelet count at discharge	132700.00	56831.22	119000.00	23000.00	340000.00
Least platelet count	43883.00	36051.89	34500.00	1000.00	256000.00

TABLE 3:

	Mean	SD	Median	Minimum	Maximum
Total Bilirubin	1.58	1.82	.88	.20	8.96
AST	203.96	320.99	123.00	33.00	2880.00
ALT	122.77	140.63	96.00	19.00	1250.00

 Distribution of LFT

Discussion:

The pathogenesis of liver involvement in dengue fever is still unknown but probable explanation could be an adverse effect of the host immune response that is directly proportional to the initial viral burden. In most patients, the effect is mild and full recovery is usual with supportive care.

Our patients had markedly elevated serum transaminases at values above 5 times the upper limit of normal and the AST levels were higher than ALT as found in the few case reports of dengue associated ALF.[26,27].The AST levels are increased than ALT in the other mild form of dengue hepatitis.[14,15,28] The AST had been reported to peak at about five to six days after the onset of illness and the ALT falls behind AST in the disease process[14].There was no mixed infection with hepatitis B or C in our patients in spite of being they are common in our region. Two other studies revealed that hepatitis B or C mixed infection did not affect the level of liver injury.[14, 15].

Some studies showed high ALT levels in dengue patients with chronic hepatitis B as compared to that without [28, 29] . However the studies did not show any

adverse effect of higher transaminases level on the coagulation profile or severity of hepatitis and comlications.[28]

In our study, liver injury was seen in both men and women and the disease was self-limiting, and there were no cases of acute liver failure. The liver enzymes were ranging from mild increase up to 20-30 times the normal values. We have observed that the thrombocytopenia and haemorrhagic manifestations were associated with severity of liver cell failure. Therefore, the use of liver tests to assess the degree of liver injury is of immense importance, may be used as parameters to assess severity for DHF and DSS.

In our study the hepatic involvement is mild to moderate and there were no cases of fulminant hepatic failure. There was no mortality seen in our patients in with or without liver involvement. Platelet count gradually decreased as diseases progress and returned to normal level once fever subsided. Bleeding manifestations are commonly seen when platelet count was less than10000Cu mm.

In our study 26 patients developed ascites or pleural effusion or both, which might have occurred due to plasma leakage, decreased oncotic pressure and volume overload. Plasma leakage which occurs due to endothelial dysfunction in dengue illness can leads to hypoalbuminemia and proteinuria[4,30,31,32].

In our series all patients improved without any complications. This is in when compared to studies conducted in children which reported 50–66% mortality [15,33].The better outcome in dengue fever in adults may be due to the increased mortality from dengue fever in children.[7,33].The host risk factors for severe dengue are young age, female gender, high body mass index and certain host genetic variants. The viral factors were the virus strain, and a secondary dengue infection[30].

Dengue illness in adults naturally runs a benign and self-limiting course. Transient mild-to-moderate transaaminase elevation is common. LFT are done on 3 and 8th day and may be repeated after 3 week if needed otherwise repeated LFT are not required. Serology for hepatitis is required only when viral hepatitis suspected or persistent liver damage on follow up.

In conclusion Dengue fever has wide range of manifestations from asymptomatic to severe form of hepatic failure. The variable severity is a big challenge to treating physician. The treatment is supportive and the prognosis is usually good. Precaution should be taken to avoid using hepatotoxic drugs to worsen the liver injury.

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