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ORIGINAL ARTICLE

CORRELATION OF LIVER FUNCTION TEST ABNORMALITIES WITH CLINICAL OUTCOMES IN PATIENTS WITH FEBRILE THROMBOCYTOPENIA: A CROSS SECTIONAL STUDY

Prakash Kikkeri Gowdaiah[1], Jacob Joseph[2], Sandeep Sreerama Reddy[3], Swetha J[4], Eby Mathew[5]

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ABSTRACT: Febrile thrombocytopenia is a common clinical condition encountered in medical wards especially so during Dengue fever epidemics. Hepatic dysfunction is a well-recognized feature of dengue infection manifested by mild to moderate increases in transaminase levels, although jaundice and acute liver failure are generally uncommon. We undertook this cross sectional clinical study to find out the pattern of liver function test abnormalities in patients with febrile thrombocytopenia and to know whether it has any adverse clinical outcome. One hundred patients aged 18 years and above with established fever and a platelet count of <1,00,000 who were admitted to medical wards of Victoria hospital, Bangalore during the dengue epidemic between May 2013 and August 2013 were enrolled into this study. Relevant laboratory tests were done including dengue serology to establish the cause of fever and to rule out liver disorders, ITP and other hematological disorders. There were 71 male patients and 29 females with majority in the age group 21 to 40 years. 65 patients tested positive on dengue serology (IgM antibody, NS1 antigen or both), and in 24 patients no cause of fever could be established. Liver function tests were normal in 54(54%) patients. Among 46 patients who had LFT abnormalities, raised SGOT and raised ALP were the most common abnormalities present in 30% each of the patients. Raised total bilirubin was present in only 4% patients. There was no statistically significant difference in severity of thrombocytopenia in patients with LFT abnormalities as well as duration of hospital stay and requirement for platelet transfusions, when compared to patients with normal liver function. Derangement of LFT could be one manifestation of a systemic infective/ inflammatory process without any serious adverse clinical outcomes in patients with febrile thrombocytopenia.

KEYWORDS: Febrile thrombocytopenia, LFT abnormalities, Dengue fever.

INTRODUCTION: Dengue infection is a major health problem worldwide including developing countries like India. Globally the incidence of dengue has grown dramatically in the recent years. The WHO estimates that presently about two fifths of the world population is at risk for this viral infection.[1] Dengue, one of the most rapidly spreading mosquito-borne viral diseases in the world, is an acute infection caused by an arbovirus in the Flavivirus genus, and the mosquito Aedes aegypti is the vector. Epidemic dengue is a major public health problem in South East Asia, especially in India where there is a reported case fatality ratio of 3–5%.[2]

Every year during the monsoon months and later, many parts of the country witness outbreaks of dengue infection. The classical form has an incubation period of 4–8 days followed by onset of fever, generalized body ache, myalgia, arthralgia, and headache.[3] Over the past few years, atypical manifestations of dengue have been reported with multiple organ involvement.[4]

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Involvement of liver in dengue has been described in textbooks as an elevation of transaminases.[5] It is characterized by right hypochondrial pain, hepatomegaly, jaundice, and elevated aminotransferase levels peaking at ninth day and gradually running to normal within 4 weeks. Although liver is not the main target for this disease, histopathology findings include centrilobular necrosis, fatty alteration, hyperplasia of Kupffer cells, acidophil bodies, and monocyte infiltration of portal tract.[6] 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.

Since, Dengue is a systemic viral disease, involvement of liver may have prognostic implications. Hence, we undertook this study to know the extent of liver involvement in acute dengue infection and its effect on final disease outcome.

MATERIAL AND METHODS: A total of hundred patients with febrile thrombocytopenia, i.e patients with established fever aged 18 years and above with a platelet count of < 1,00,000/mm^3,who were admitted to medicine wards at Victoria hospital, Bangalore Medical College, during the dengue epidemic between May 2013 to August 2013, were included in the study. Patients with ITP, hematological disorders/malignancies, and those on chemotherapy or immunosuppressive therapy and patients with liver disorders were excluded from the study. Serological tests for detection of Dengue antibodies by ELISA and/or NS1 antigen was carried out in all the patients. When the results of either of these tests were positive, patients were considered to be currently infected with dengue virus. Test negatives were considered unconfirmed after ruling out other causes of febrile illness.

All were admitted with acute febrile illness with varying symptoms, few also had bleeding manifestations. Serial platelet count monitoring was done on 1st day, 3rd day and at the time of discharge. Other investigations which were undertaken include the hematocrit, total count, renal and liver function tests, dengue serology, smear for malarial parasite, WIDAL, chest x ray and ultrasound of abdomen and pelvis.

RESULTS:

Age in years	Gender		Total
	Female	Male	
17-20	3	5	8(8%)
21-30	8	30	38(38%)
31-40	2	18	20(20%)
41-50	9	8	17(17%)
51-60	5	5	10(10%)
>60	2	5	7(7%)
Total	**29**	**71**	**100(100%)**

Table 1: Showing Age and Sex distribution of patients studied

There were 71 male patients and 29 females with majority in the age group 21 to 40 years. (Table-1). 65 patients tested positive on dengue serology (IgM antibody, NS1 antigen or both), 3 patients were positive for vivax malaria, 6 patients showed widal positivity, leptospirosis was the

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diagnosis in 2 patients, and in 24 patients no diagnosis could be established. (Table 2.) Probably these patients might not have developed sufficient dengue antibody titres at the time of testing.

Etiology	Gender		Total (n=100)
	Female (n=29)	Male (n=71)	
Dengue	21	44	65
Malaria	00	03	03
Enteric fever	02	04	06
Leptospirosis	01	01	02
Others (Etiology not established)	10	14	24

Table 2: Showing Etiology of Fever

The commonest symptom was fever, followed by headache, myalgia, vomiting and joint pains as shown in Table 3. Bleeding manifestation was noticed in only14% of patients. Majority of patients (79%) had normal physical examination. Hepatosplenomegaly was the commonest physical finding (10%) followed by ascites and pleural effusions in 9% of patients as shown Table 4. Majority (97%) of patients were hospitalized for 3 to 7days.

	Gender		Total (n=100)
	Female (n=29)	Male (n=71)	
Fever	29	71	100(100%)
Headache	17	51	68(68%)
Myalgia	14	36	50(50%)
Vomiting	11	33	44(44%)
Joint pains	7	21	28(28%)
Abdominal pain	4	13	17(17%)
Bleeding	3	11	14(14%)
Loose stools	1	5	6(6%)
Cough	0	6	6(6%)
Breathless	1	1	2(2%)
Altered sensorium	0	1	1(1%)

Table 3: Showing Clinical manifestations (Symptoms) of patients studied

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Systemic	Gender		Total
	Female	Male	
Normal	23	56	79
Hepatosplenomegaly	3	7	10
Pleural effusion + Ascites	1	8	9
Hepatomegaly	2	2	4
Basal crepts	0	4	4
Ascitis	0	4	2
Splenomegaly	1	0	1

Table 4: Showing clinical manifestations (signs) of patient studied

On admission majority (89%) of patients had hematocrit in 30-50 range. 71% had hemoglobin > 12gm% and none had features of leucopenia or pancytopenia. The initial (on the day of admission) platelet count was < 20,000 in 26% of patients, between 20,000 to 50,000 in 40% and 50,000 to 100000 in 32% of patients. The mean platelet count improved significantly during hospital stay in all the patients as shown in Table 5.

Platelet Count	Min-Max	Mean ± SD
Initial	4000.00-120000.00	41370.00±26921.76
3rd day	10000.00-130000.00	49465.00±29179.11
5th day	10000.00-180000.00	76928.57±37165.62
At discharge	75000.00-265000.00	143250.00±38133.84

Table 5: Showing change in mean Platelet count at various time intervals of hospital Stay

Liver function tests were normal in 54 (54%) patients. Among 46 patients who had LFT abnormalities, raised SGOT and raised ALP were the most common abnormalities present in 30% each of the patients. Raised total bilirubin was present in only 4% patients. (Table 6, Fig 1). But there was no correlation between the severity of thrombocytopenia and derangement of LFT as shown in Table 7, Fig 2. (P value= 0.408). There was also no correlation between deranged liver function and duration of hospital stay. 95% of patients in both groups were discharged within one week.

LFT	Gender		Total (n=100)
	Female (n=29)	Male (n=71)	
Normal	15	39	54(54%)
Raised ALP	19	11	30(30%)
Raised SGOT	7	23	30(30%)
Raised total bilirubin(TB)	0	4	4(4%)
Raised SGPT	4	14	18(18%)

Table 6: Showing liver function test (LFT) results of patients studied

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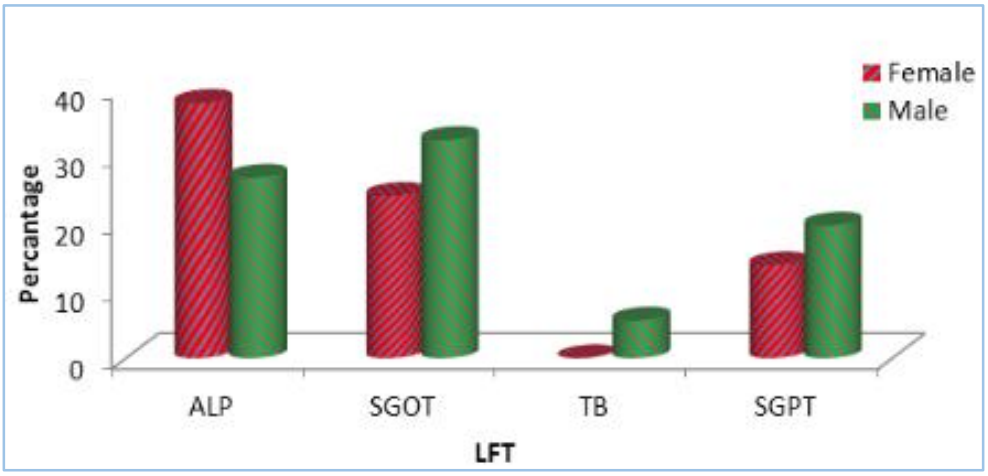

Figure 1: Showing different patterns of abnormal LFT

Liver function test (LFT)	Platelet count				Total
	<10000	10000-20000	20000-50000	>50000	(n=100)
Normal LFT	33.3%	50%	50%	64.7%	54
Abnormal LFT	66.7%	50%	50%	35.3%	46
Total	**100%**	**100%**	**100%**	**100%**	**100**

Table 7: LFT findings according to distribution of baseline platelet count

P=0.408, Not Significant, Fisher Exact test.

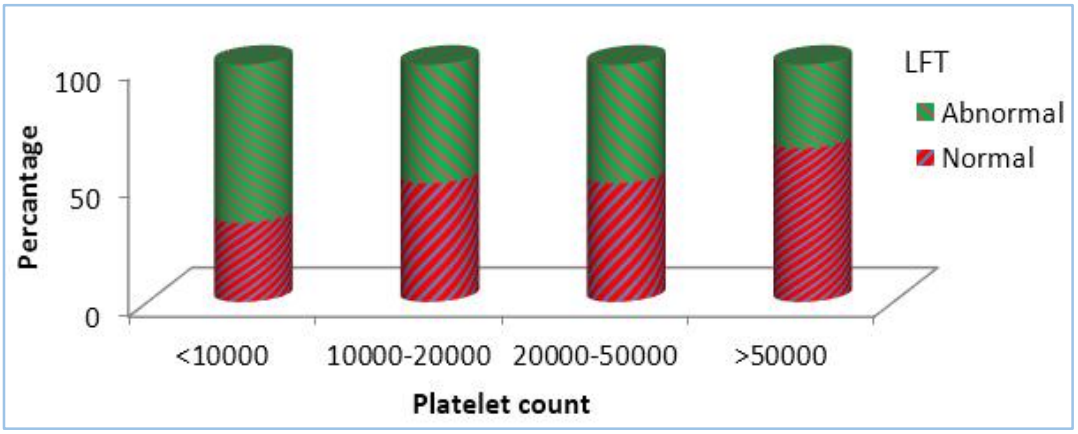

Figure 2: Showing baseline platelet count in relation to LFT

In this study patients with deranged LFT actually received less units of platelet transfusion than patients with normal liver function as shown in Table 8. Once again establishing the fact that derangement of LFT could be one manifestation of a systemic infective /inflammatory process without any serious adverse clinical outcomes in patients with febrile thrombocytopenia.

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Platelet Transfusion	LFT		Total number of patients
	Normal	Abnormal	
No platelet transfusion	51.9%	63%	57
1-5units	1.9%	8.7%	5
6-10 units	40.7%	17.4%	30
>10 units	5.6%	10.9%	8
			n=100

Table 8:Comparing number of units of platelets transfused in patients with normal/abnormal LFT

P=0.036*, Significant, Fisher Exact test

DISCUSSION: This study was undertaken to study the clinical and hematalogical profile of patients who presented with febrile thrombocytopenia, with particular emphasis on hepatic dysfunction and its implications toward clinical outcome. Accordingly, it was found that there were varying presentation of symptoms and nonspecific findings on clinical examination. A study which was published from north India in 2012.[7] supports the findings of our study in this context wherein they stated that it can have varied and multi-systemic manifestations which can go unrecognized. Clinicians should have a high index of suspicion for atypical manifestations. In a study which was done in children in Delhi, clinical features of DHF varied from epidemic to epidemic. Hepatic dysfunction with increased levels of serum enzymes was common in DHF.[8]

Thrombocytopenia and elevated transaminases were observed in patients with classic dengue fever. Most laboratory abnormalities started on the 3rd day but were more evident on the 5th day with restoration of values by the 11th day; this was more prominent in under 15-year-olds and with the more severe clinical forms.[9]

Clinical and experimental observations suggest that liver involvement occurs during dengue infections. Clinical evidence includes hepatomegaly and increased serum liver enzymes, with liver involvement being more pronounced in the more severe forms of infection. Dengue viralantigens have been found within hepatocytes, and the virus appears to be able to replicate in both hepatocytes and Kupffer cells, and dysregulated host immune responses may play an important causative role in liver damage. Modulating these immune responses may have a therapeutic potential. There are limitations in the investigation of liver involvement in dengue infection as the immunopathological lesions in the liver are difficult to study in patients with thrombocytopenia and coagulative dysfunction.[10]

Our study showed significant derangement in liver function tests with elevated transaminases and alkaline phosphatase in patients with febrile thrombocytopenia. AST (SGOT) levels were elevated in more number of patients than ALT (SGPT). But deranged bilirubin values were found in only 4% of patients. Sumathi K et al.[11] in their study also found similar values. But, there was no correlation between deranged LFT and severity of thrombocytopenia as well as other clinical parameters like duration of hospital stay and requirements for platelet transfusions.

CONCLUSION: It can be concluded from our study that liver function abnormalities occur in nearly 50% of patients having febrile thrombocytopenia, and that derangement of LFT could be one manifestation of a systemic infective /inflammatory process without any serious adverse clinical outcomes.

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AUTHORS:

1. Prakash Kikkeri Gowdaiah
2. Jacob Joseph
3. Sandeep Sreerama Reddy
4. Swetha J.
5. Eby Mathew

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore.
2. Postgraduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore.
3. Postgraduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore.
4. Postgraduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore.
5. Postgraduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Prakash Kikkeri Gowdaiah,
Associate Professor,
Department of Medicine,
Bangalore Medical College and Research Institute,
Bangalore-2
Email: kikkeri47@yahoo.com

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