

Study Of Liver Dysfunction In Acute Dengue Infections In A Tertiary Care Hospital

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ABSTRACT

Introduction

Dengue or break bone fever caused by a RNA virus of arbovirus family is spread by Aedes mosquitoes. It has wide range of presentations ranging from asymptomatic to dengue hemorrhagic fever with or without shock. In severe conditions it involves heart, liver and brain with liver as the most common organ involved. Clinical outcome is related to multiple parameters including high PCV and low platelet count. The frequency of liver involvement shows variable results with hepatomegaly found in 4 – 52% of cases. The association between liver injury with PCV and platelet count is not well studied.

Objectives

- 1. To study the transaminase level in dengue infections as an evidence of hepatic dysfunction.*
- 2. To study the association of liver transaminases with hemodynamic factors like hemoglobin, packed cell volume, platelet count in dengue patients with liver dysfunction.*

Methodology

This is a retrospective cross sectional study conducted using the patient data of the dengue outbreak in August to October 2017 at Vinayaka Missions Medical College and Hospital, Karaikal. All dengue patients (n=201) diagnosed with positive dengue Non Structural-1 or IgM positive were included. After getting institute ethical clearance, AST, ALT, PCV, Platelet count and baseline data were collected.

Results

Among 201 dengue infected cases, 62% were males and 38% were females. Among them 31% and 45% were having elevation of AST and ALT respectively. Major proportion of those with elevated liver transaminases were middle aged and among the transaminases AST was found to be predominantly raised than ALT. Platelet was significantly decreased in dengue patient with high ALT and high AST compared to that of normal ALT and AST counterparts. Platelet count showed statistically significant negative correlation with AST and ALT levels. PCV showed a significant negative correlation with AST levels.

Conclusion

Increase in AST and ALT levels shows the involvement of liver in the dengue patients. A negative correlation was seen between liver enzymes and platelet levels implying a common mechanism for both liver injury and low platelet count. Further studies are needed to find their basis, which may help in early detection of complications and in applying treatment regimens for dengue patients.

Key Words: AST-Aspartate transaminase, ALT-Alanine transaminase, HCT-Hematocrit

Introduction

Dengue virus is a RNA virus of arbovirus family spread to humans by Aedes mosquitoes. Dengue or break bone fever caused by dengue virus manifests with wide clinical presentations ranging from asymptomatic to classical dengue fever or dengue hemorrhagic fever with or without shock.¹ Uncommon manifestations such as cardiomyopathy, hepatic failure and neurological disorders have also been reported.²

Liver is the most common organ involved in dengue viral infection. The frequency of liver involvement shows variable results with hepatomegaly found in 4 – 52% of cases³. Right hypochondrial discomfort, liver enlargement, and raised serum aspartate transaminase (AST) and alanine transaminase (ALT) levels are all signs of dengue viral infection affecting the liver. Abdominal pain (18%-63%), nausea, vomiting (49%) and anorexia (58%) were the most common clinical symptoms linked with liver dysfunction in dengue infection.⁴ Increased Hematocrit (PCV: packed cell volume) is usually observed in dengue due to dehydration in response to plasma leakage. Thrombocytopenia and platelet dysfunction are the potential variables related to the clinical outcome of the dengue cases. The association between liver transaminases and hemodynamic factors (PCV and platelet count) is not well studied.

Objectives:

1. To study the transaminase level in dengue infections as evidence of hepatic dysfunction.
2. To study the association of liver transaminases with hemodynamic factors like hemoglobin, packed cell volume, platelet count in dengue patients with liver dysfunction.

Review Of Literature

Gandhi K et al, conducted a study of Liver Function Test in south Indian population who are affected with dengue. They reported that liver damage with alteration of aminotransferases is a common complication of dengue and valuable marker for monitoring these patients.¹⁰

Treeraprasertsuk S et al, this study revealed the predictors of liver complications, associated failure of other organs and also high levels of AST are seen in febrile stage of dengue.¹¹

Souza LJD et al, reported that around 65.1% patients affected with dengue showed abnormal aminotransferase levels.¹²

Dengue hemorrhagic fever, severe dengue, and the clinical significance and selective value of AST or ALT were evaluated by Lee K et al. According to the findings, there was a considerable overlap in AST and ALT values between patients with Dengue Fever and Dengue Hemorrhagic Fever, as well as between patients with Dengue Fever and Dengue Hemorrhagic Fever.¹³

In this study, Ojha A et al. addressed the mechanism of thrombocytopenia in dengue infections by establishing a direct link between platelet activation and depletion. On day 4, the platelet count dropped dramatically, but by day 10, it had recovered. More dengue virus-activated platelets were phagocytosed by monocytes in considerable numbers. In the presence of platelet activation inhibitor and prostacyclin, platelet lysis occurs.¹⁴

Jayanthi KH et al, conducted a study on correlation between platelet and non-hemorrhagic complications. His study concludes that platelet count can be used to predict the complication and duration of hospital stay.¹⁵

Methodology

The research was carried out at Vinayaka missions medical college and hospital, Karaikal, Pondicherry. We collected dengue positive patient's data from medicine In Patients records. 201 patients were included in our study.

Research committee and ethical clearance:

The study was conducted after obtaining the institutional research and the ethical committee clearance.

Study setting and participants:

We collected laboratory data (biochemical and pathological) of dengue positive patients in Department of General Medicine, Vinayaka Missions Medical College and Hospital, Karaikal, Puducherry, 609609.

Study design: Retrospective cross-sectional study

Study duration: 3 months.

Inclusion criteria:

1. All dengue Non-Structural-1 or IgM positive cases are included in this study.
2. Both males and females were included in this study.

Exclusion criteria :

1. Already suffering from chronic liver disease
2. Bleeding disorders like Idiopathic Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura and coagulation disorders
3. Chronic alcoholics
4. Post splenectomy patients
5. Those who are on Anti-Tubercular drugs
6. Chronic kidney disease patients

Statistical analysis:

Data was presented as Mean \pm SD. Comparison of variables was done by student t test. Correlation among the variables was done by Pearson correlation analysis. A P value <0.05 was taken as significant. Data analysis by SPSS version 24.

Results

We enrolled 201 cases of dengue infection based on diagnostic criteria. Among 201 dengue infected cases, 62% (n=124) were males and 38% (n=77) were females (Fig 1). Based on serum ALT levels, dengue patients were divided as Group 1 (normal ALT) and Group 2 (high ALT). Ninety (45%) cases showed normal serum ALT levels and 111 (55%) cases were found to have elevated ALT levels (Fig 2). In Fig 3, 62 (31%) cases showed normal AST and were included in Group 3 and 139 (69%) cases showed elevated AST were grouped as Group 4. Among the patients with dengue infection, platelet count was found to be significantly decreased in group 2 compared to group 1 (Table 1). AST had a strong positive link with ALT in the 201 dengue patients, while platelets had a substantial negative correlation with ALT (Table 2). Serum ALT was also negatively correlated PCV (Table 3). During comparison of parameters between group 3 and group 4, found the significant decrease in platelet counts in group 4 (Table 4). Pearson analysis, done on all dengue cases, revealed that serum AST levels were negatively correlated with platelet count and PCV (Table 5) Pearson analysis, done on patients with group 4 alone, showed that serum AST levels were negatively correlated with platelet count and PCV (Table 6).

Fig 1: Gender wise distribution of liver involvement in dengue infected cases:

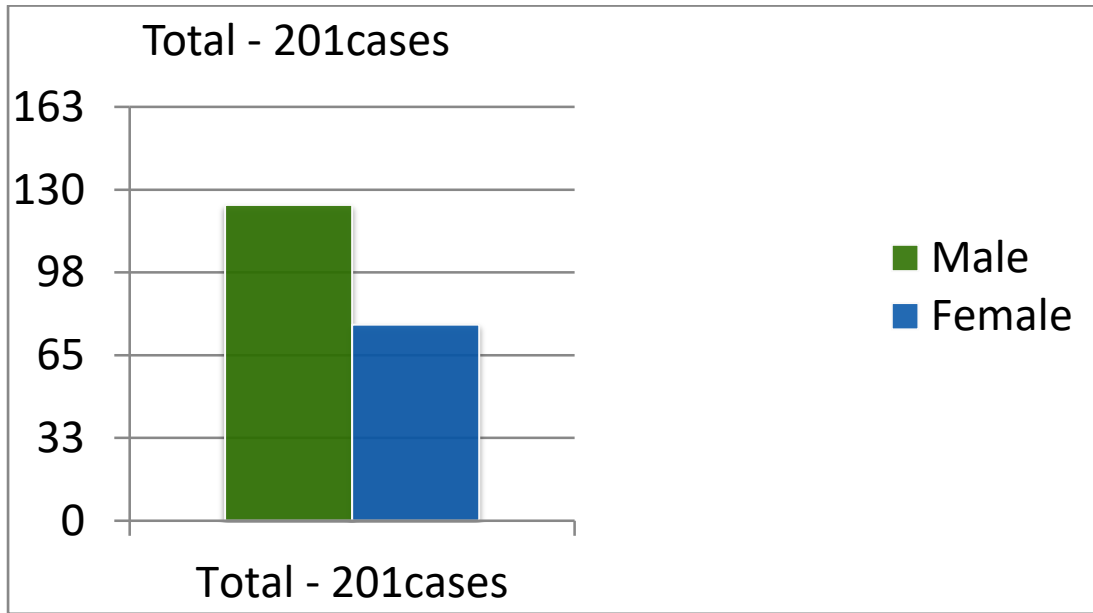
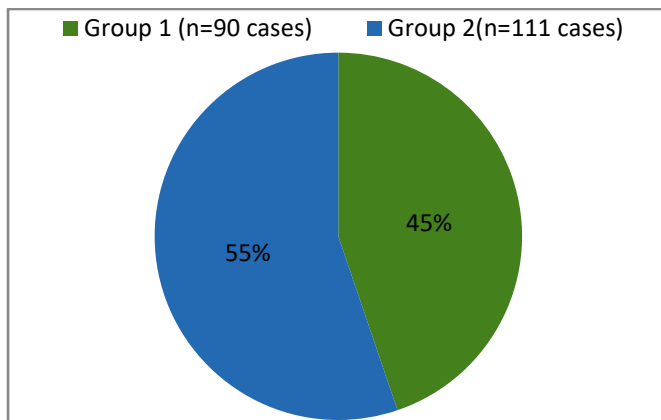


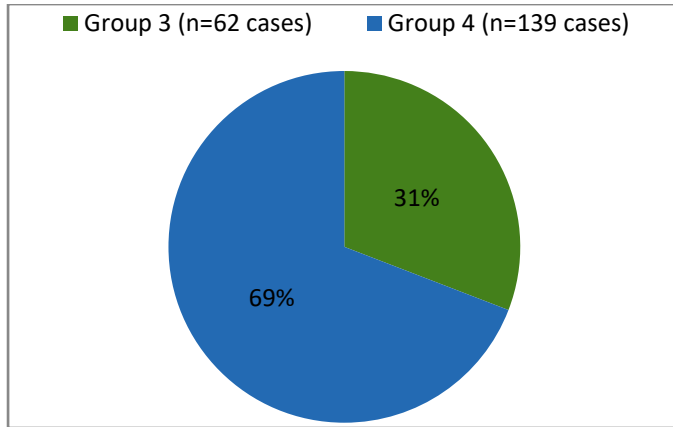
Fig 2: Proportion of dengue infected patients with normal and high ALT.



Group 1- Dengue patients with normal ALT

Group 2- Dengue patients with elevated ALT.

Fig 3: Proportion of dengue infected patients with normal and high AST.



Group 3 Dengue patients with normal AST

Group 4 Dengue patients with elevated AST.

Table 1: Comparison of hemodynamic factors between the Dengue patients with normal ALT (group 1) and high ALT (and group 2)

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Age (years)	30.1 ± 15.1	30.6 ± 16.4	0.825
Hemoglobin (gm/dl)	12.8 ± 1.8	13.1 ± 2.1	0.218
PCV (%)	38.2 ± 5.1	39.2 ± 6	0.221
Platelet (thou-sand/cu.mm)	142.6 ± 57.9	95.9 ± 65.6	0.000*
AST (IU/L)	40 ± 17	250± 584	0.000*

Group 1- Dengue patients with normal ALT

Group 2- Dengue patients with elevated ALT

pvalue<0.05 was taken as significant.

Table 2: Correlation between high ALT and other parameters among all dengue infected cases (n = 201 cases)

	r value	p value

Age	-.077	0.276
Hemoglobin	-.097	0.17
PCV	-.129	0.068
Platelet	-.226	0.001*
AST	.975	0.000*

r- correlation co-efficient detected by pearson correlation analysis.

pvalue<0.05 was taken as significant.

Table 3: Correlation between ALT and other parameters among dengue infected cases with high ALT (group 2) (n = 111)

	r value	p value
Age	-.110	0.25
Hemoglobin	-.17	0.07
PCV	-.211	0.02*
Platelet	-.163	0.08
AST	.977	0.00*

r- correlation co-efficient detected by pearson correlation analysis. pvalue<0.05 was taken as significant.

Table 4: Comparison of hemodynamic factors between the Dengue patients with normal AST (group 3) and high AST (and group 4)

	Group 3 (Mean \pm SD)	Group 4 (Mean \pm SD)	p value
Age	32.1 \pm 14	29.6 \pm 16.5	0.289
Hemoglobin	12.8 \pm 1.9	13.0 \pm 2.0	0.698
PCV	38.4 \pm 5.1	38.8 \pm 5.9	0.628
Platelet	147.5 \pm 56	103.1 \pm 66.1	0.000*
ALT	24.5 \pm 10.4	112 \pm 205.7	0.000*

Group 3 – Dengue patients with normal AST
 Group 4 – Dengue patients with elevated AST
 pvalue<0.05 was taken as significant.

Table 5: Correlation between AST and other parameters among all dengue infected cases (n = 201 cases)

	r value	p value
Age	-.089	0.20
Hemoglobin	-.127	0.07
PCV	-.163	0.02*

Platelet	-.211	0.003*
ALT	.975	0.000*

r- correlation co-efficient detected by pearson correlation analysis. pvalue<0.05 was taken as significant.

Table 6: Correlation between high AST and other parameters among dengue infected cases (group 4) (n = 139)

	r value	p value
Age	-.088	0.30
Hemoglobin	-.159	0.062
PCV	-.201	0.018
Platelet	-.185	0.03*
ALT	.975	0.00*

r- correlation co-efficient detected by pearson correlation analysis.

P value <0.05 was taken as significant.

Discussion

One of the causes of acute liver failure is dengue fever.⁸ The National Vector Borne Disease Control Programme (NVBDCP) reported over 100,000 laboratory confirmed dengue cases in 2016, and the majority of histopathology reports with dengue human death cases indicate that the liver, spleen, and lymph nodes are infection target organs.^{18,19} Among 201 dengue infected cases, 62% were males and 38% were females. Similar findings were also reported by Wali et al., in which nearly twice the number of male patients were infected compared to females.²⁰ Among the dengue infected cases, major proportion of those with elevated liver transaminases were middle aged.

In this study we studied the changes in the serum level of AST and ALT levels, because they're known to be markers of liver cell injury.¹⁶ Among them AST was found to be predominantly raised than ALT which is in concordance with the study done by Kumar S et al.¹⁷ Gandhi K et al, conducted a study of LFT in south Indian population who are affected with dengue. They reported that liver damage with alteration of aminotransferases is a common complication of dengue and valuable marker to monitor these patients.¹⁰ This study and ours are comparable. Heparansulphate, which plays a key role in the dengue virus's entry into liver (HepG2) cells, is thought to be the reason of liver damage in dengue infection.²¹ A cell must have viral entrance and a suitable environment for the invader to flourish inside the host cell in order to be infected by a virus, and this property is impacted by viral serotype, strain, and cell type. G2 phase cells, for example, are more susceptible to infection and boost virus replication.²²

Platelet count was significantly decreased in dengue patients with high ALT and high AST (In table 1 and table 4) implying that the patients with liver cell injury had low platelet count compared to those without liver cell damage.

During correlation analysis, we observed that platelets had statistically significant negative correlation with AST and ALT levels. Low platelet counts are caused by the dengue virus, which can damage bone marrow progenitor cells directly or indirectly by suppressing their function, reducing the proliferative ability of hematopoietic cells.²³ This makes us to hypothesize that the molecular mechanisms leading to lowering of platelets in dengue infection may have a role in causing liver cell injury.

Endothelial cell barrier integrity and functions are expected to be impacted by a complex interplay amid the virus, the host immune response, and endothelial cells, resulting in plasma leakage. Dengue virus-induced autoantibodies have been implicated in the pathophysiology of dengue hemorrhagic fever in a number of investigations. Human and mouse antibodies to NS1 have been found to attach to host cells such as endothelial cells and platelets in a variety of investigations. Antibodies bind to endothelial cells, causing them to apoptosis. These antibodies' target compounds have yet to be discovered. The passive transfer of these antibodies into mice resulted in a variety of changes, including bleeding and coagulopathy, raised liver enzyme levels, and endothelial cell death, all of which seemed to be mediated by nitric oxide and caspase. Because dengue hemorrhagic fever is self-limited and patients recover quickly without showing signs of autoimmune illness, the significance of these antibodies in the pathogenesis of DHF in people is unknown.²⁴

In a group of dengue infected patients with liver injury, defined by elevated AST levels, packed cell volume also showed a significant negative correlation with AST levels. (PCV is increased due to dehydration in response to plasma leakage. As AST was correlated significantly with PCV, a possible ischemic liver injury also play a role in dengue patients.)

In this study, Ojha A et al. addressed the mechanism of thrombocytopenia in dengue infections by establishing a direct link between platelet activation and depletion. On day 4, the platelet count dropped dramatically, but by day 10, it had recovered. More dengue virus-activated platelets were phagocytosed by monocytes in considerable numbers. Platelet lysis occurs when platelet activation inhibitors and prostacyclin are present.¹⁴

Conclusion

Patients with dengue infection showed liver injury in 45% of cases (as per ALT levels) and 31% (as per AST levels). Most of them are males with middle aged group. Platelets were low among the patients with liver involvement compared to those with normal liver functions. Liver transaminases showed negative association with platelet and PCV. Further studies are required to establish this association as this will be useful in better understanding of the pathogenesis and to take preventive measures.

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