

Study of co-relation between Transaminitis and fall in platelet counts in patients with Dengue Fever and its association with severity of clinical presentation

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Abstract: *Background:* Dengue fever presents with varied presentations which include liver cell injury. This Liver injury manifests as Transaminitis which correlates with clinical severity. A severity of disease is associated with increased transaminases and sequential fall in platelet count which has been observed in this study. *Objectives:* To study the co relation between raised Liver enzymes and Thrombocytopenia in clinical spectrum of Dengue fever. *Methods:* In a tertiary referral hospital, 100 confirmed patients were enrolled and observational study was conducted over a period of 18 months. Detailed history, Physical examination done were recorded. Serial platelets counts and Aminotransferase levels were done. Patients were followed up till discharge. Data was analysed using appropriate statistical tests. *Results:* SGOT was mildly increased in 28% of patients, moderately increased in 34% of patients, and severely increased in 38% of patients and SGPT was observed normal in 5%, mildly increased in 47% of patients, moderate increased 22% of patients, and severe increased in 27% of patients. Strong corelation was observed between severity of Transaminitis and Thrombocytopenia ($p<0.001$) *Conclusion:* Transaminitis is an important prognostic marker in Dengue fever and can be used early to distinguish between Dengue fever, Dengue hemorrhagic fever and Dengue shock syndrome at time of clinical presentation. The raise of SGOT and SGPT correlated proportionately with the Thrombocytopenia and the spectrum of disease severity.

Keywords: Dengue fever, Transaminitis, Thrombocytopenia, Dengue shock syndrome.

Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries [1]. Annually 100 million cases of dengue fever and half a million cases of DHF occur worldwide. Early recognition and prompt initiation of treatment are vital if disease related morbidity and mortality are to be limited [2].

Liver is known to be affected in dengue fever. Degree of Hepatic damage ranges from mild injury with mild elevation of serum transaminases to severe injury with jaundice and subsequent Fulminant Hepatic failure [3]. Thrombocytopenia

is also a feature of Dengue fever and its sequential fall co relates with the disease severity [4].

So the aim of our study is to evaluate degree of liver injury in terms of raised transaminases [5] level and to study the co relation between raised Liver enzymes and Thrombocytopenia in clinical spectrum of Dengue fever.

Material and Methods

This is an observational study conducted in Department of General Medicine in Shifaa hospital, Queen's road Dar-us-salam Building, Bangalore.

Study Population: Patients with Dengue Serology positive (NS1 antigen, IgM, and IgG antibody) admitted in shifaa hospital during the said period selected. (n=100)

Study duration: This study will be conducted for a period of 18 months from Dec 2017 to May 2019.

Ethical Clearance: The study conducted after obtaining permission from Shifaa hospital ethical committee and informed written consent taken from Patient and his relatives.

Inclusion criteria:

1. Patient admitted with Dengue NS 1 Ag positive and IgM antibody positive
2. Patient admitted in Shifaa hospital having fever more than 38.5 °C

Exclusion criteria:

1. Age less than 12 years.
2. Preexisting substantial chronic liver, kidney or heart disease.
3. Patients with history of hematological disorders.

Sample size: According to study conducted by Sauza L.J. et al [7] proportion of patients with altered aminotransferase levels was 44.5% in dengue cases so $p=44.5\%$

Samples size can be calculated by formula

$$\text{Sample size} = n = 4Pa/e^2$$

$$\text{Where } p = 44.5\% = 0.445; a = 1 - p = 0.555$$

$$\text{Considering absolute error } e = 10\% = 0.1$$

$$N = 4Pa/e^2 = 4 \times 0.445 \times 0.555 / 0.1 \times 0.1$$

$$N = 98.79$$

$$N = 100$$

Collection of data: For study data collected through

- 1) Patients particulars and history including Name, age, Gender and symptoms such as Fever, myalgia, Headache.
- 2) Physical Findings including patient weight, height and Body mass index, temperature, pulse rate, blood pressure, bleeding manifestation, tourniquet test, liver enlargement
- 3) Laboratory examinations consisting of Hemoglobin, Hematocrit, Platelet count, dengue serology, Serum ALT and AST were collected at admission.

It is an Observational study over a period of 18 months. A total of 100 patients admitted to Shifaa hospital. Detailed history taken, Physical

examination done, withdrawal of sample at time of admission for platelets count and aminotransferase level done.

The data collected was entered in Microsoft Excel and Statistical analyses were performed using the Statistical Package for Social Science (SPSS ver 18.5) software and compared co-relation with of fall in platelet count and serum Transaminits with each other and with clinical presentation by using Chi-square test of significance, student 't' test and Pearson Correlation Coefficients was calculated to determine whether there was any correlation between the Platelet Count vs SGOT and SGPT.

Results

Out of 100 patient's gender wise distribution observed was 69 were male patients and 31 were female patients. 87% patients were diagnosed to be DF and 10% patients were diagnosed to be DHF and 3% patients were diagnosed to be DSS. Clinical symptoms in overall patients observed to be Fever (100%), abdominal pain in 81% of patients, Headache (87%), arthralgia (74%), vomiting (63%), Myalgia (61%), Retro orbital pain (61%), diarrhea (30%) and rash 20% of patients. Other clinical manifestation observed to be Pleural effusion 21%, Ascites 9% and Icterus 6% of patients.

As Thrombocytopenia was observed in all patients and PCV rose (>54%) was observed to be more in patients presented with DSS than DHF and DF. Leucopenia (<4000) was observed to be in 51% of patients. Bleeding manifestation was observed in 11% of Patients, which is described as epistaxis in 2% of patients, gum bleeding in 5% of patients, Malena in 1% of patients, p/v bleeding in 3% of patients, and 89% of patients were observed with no bleeding manifestation.

SGOT was mild increased observed to be in 28% of patients, moderate increased in 34% of patients, and severe increased observed to be in 38% of patients and SGPT was observed normal in 5%, mildly increased in 47% of patients, moderate increased 22% of patients, and severe increased observed to be in 27% of patients (Table 1).

Table-1: Distribution of Platelet Count and SGOT values among the Study population

| Time | Platelets | SGOT(IU/L) | | | Total | χ ² value | P value |
|-------|---------------|------------|---------------|-------------|--------|----------------------|---------|
| | | Mild Rise | Moderate Rise | Severe Rise | | | |
| Day 1 | 10000-20000 | 0 | 0 | 5 | 5 | 26.732 | <0.001 |
| | | .0% | .0% | 100.0% | 100.0% | | |
| | 20001-50000 | 4 | 11 | 17 | 32 | | |
| | | 12.5% | 34.4% | 53.1% | 100.0% | | |
| | 50001-100000 | 18 | 22 | 16 | 56 | | |
| | | 32.1% | 39.3% | 28.6% | 100.0% | | |
| | 100001-150000 | 6 | 1 | 0 | 7 | | |
| | | 85.7% | 14.3% | .0% | 100.0% | | |
| | Total | 28 | 34 | 38 | 100 | | |
| | | 28.0% | 34.0% | 38.0% | 100.0% | | |

Severe Thrombocytopenia (less than 20000) was associated with severe rise of SGOT in 100% of patients. Moderate Thrombocytopenia (less than 50000) was associated with SGOT mild rise in 12% patient's moderate rise in 34% patients and severe rise in 53% patients. Mild Thrombocytopenia (less than 1 lac) Thrombocytopenia were associated with SGOT mild rise in 32% patients, moderate rise in 39%, severe rise in 29% patients.

Platelet counts of 100000-150000/cumm were associated with SGOT mild rise in 85% patients, moderate rise in 14% of patients. (p<0.001). As it is evident from the above analysis, the severity of clinical features correlated with fall in the platelet count and raise in liver enzymes. Patient with

platelet counts 10000-20000/cumm were associated with severe rise of SGPT in 100%. Platelet counts of 20000-50000/cumm were associated with SGPT mildly raised in 34% of patient, moderate rise in 21% of patients and severe rise in 43% of patients. Platelet counts of 50000/cumm -100000/cumm were associated with SGPT mild rise in 56% patients, moderate rise in 26% of patients and severe rise in 14% of patients, Platelet counts of 100000/cumm -150000/cumm were associated with SGPT mild rise in 85% patients. This result shows P value less than 0.001 which means statistically significant i.e. results shows more severe fall in platelet count was associated with more severe rise of SGPT. (p<0.0010) (Table 2).

Table-2: Distribution of Platelet Count and SGPT values among the Study population

| Time | Platelets | SGPT(IU/L) | | | | Total | χ ² value | P value |
|-------|---------------|------------|-----------|---------------|-------------|--------|----------------------|---------|
| | | Normal | Mild Rise | Moderate Rise | Severe Rise | | | |
| Day 1 | 10000-20000 | 0 | 0 | 0 | 5 | 5 | 31.431 | <0.001 |
| | | .0% | .0% | .0% | 100.0% | 100.0% | | |
| | 20001-50000 | 0 | 11 | 7 | 14 | 32 | | |
| | | .0% | 34.4% | 21.9% | 43.8% | 100.0% | | |
| | 50001-100000 | 3 | 30 | 15 | 8 | 56 | | |
| | | 5.4% | 53.6% | 26.8% | 14.3% | 100.0% | | |
| | 100001-150000 | 1 | 6 | 0 | 0 | 7 | | |
| | | 14.3% | 85.7% | .0% | .0% | 100.0% | | |
| | Total | 4 | 47 | 22 | 27 | 100 | | |
| | | 4.0% | 47.0% | 22.0% | 27.0% | 100.0% | | |

This is an observational study, following observations are made from our study. Serum levels of SGOT at time of presentation to hospital in DF patients were observed to be raised mildly in 32% of patients, moderate rise in seen in 36% of patients, and severe rise in 37% of patients. In DHF patients SGOT level observed to be raised mildly in 20% of patients, and moderate rise in 80%. In DSS patient SGOT level observed to be raised severely in 100%. These results were suggestive of severe rise of SGOT at initial presentation to hospital were associated with increased severity of disease. Serum levels of SGPT at time of presentation to hospital in DF patients were raised mildly in 50% of patients, moderately raised in 21% of patients and severe rise in 23% of patients.

In DHF patients SGPT level were observed to be raised mildly in 30% of patients, moderate rise in 20% of patients, and severe rise in 66% of patients. In DSS patients SGOT levels found to be raised moderate in 33% of patients, severely in 66% of patients. From these results it is observed that severe rise of serum level of SGPT were associated with increased severity of disease at time of Presentation hospital. The severity of the disease correlated inversely with thrombocytopenia and positively with Transaminitis.

Discussion

Ali K. Ageep and Abu elgasim S. et al. a Correlation study between clinical manifestation of dengue fever and degree of liver injury. Studied 633 confirmed dengue case, among them 248 were male and 319 were female, in this study 13.2% of patient had no increase in transaminases level (Grade 0). 63.8% presented mild alteration in liver enzymes levels (grade -1,) 17.9% presented grade -2 liver involvements. 3.9% patients had progressed to acute hepatitis (grade 3) and 1.1% had severe liver damage with fulminant hepatic failure. 86% of them were liver enzymes increased. All of them had increase in AST level and 82% patients increase in ALT [6].

Souza LJ, et al. Studied 1,585 dengue serology confirmed cases for aminotransferase changes and acute hepatitis in patients with dengue fever 44.5% presented with alteration in the aminotransferase levels 16.9% presented with

grade c liver involvement and 3.8% of patients progressed to acute hepatitis average value of AST and ALT were 93.3U/L and 86.0U/l [7].

Lee LK et al retrospectively studied and classified polymerase chain reaction positive dengue patients from 2006 to 2008 treated at Tan Tock Seng Hospital, Singapore according to WHO 1997 and 2009 criteria for dengue severity, selected 690 dengue patients, 31% had DHF and 24% severe dengue. Elevated AST and ALT occurred in 86% and 46%, respectively. Seven had AST or ALT \geq 1000 U/L. None had acute liver failure but one patient died. Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) is prominent in acute dengue illness. The World Health Organization (WHO) 2009 dengue guidelines defined AST or ALT \geq 1000 units/liter (U/L) as a criterion for severe dengue [8].

Samanta J, et al. studied an Affliction of liver in form of derangements in the liver function tests is common and may include mild elevations in serum bilirubin, elevated transaminases and derangements in serum albumin. Although asymptomatic in most cases, clinical manifestations like jaundice and acute liver failure (ALF) may occasionally complicate the clinical picture. Indeed, dengue has been implicated as an important cause of ALF in endemic countries. The present review focuses on the hepatic manifestations and the pathogenesis of the liver injury in dengue [9].

Kuo CH, et al the impact of dengue on liver function was studied by biochemical test on 125 male and 145 female patients diagnosed with this disease during an outbreak from Nov 1987 to Dec 1988 abnormal levels of AST , ALT, bilirubin , alkaline phosphatase ,GG-T were observed in 93.3%, 82.2%, 7.2 %,16.3% and 83% of patients respectively. Elevation of transaminase was mild to mod in most of cases. But was 10-fold greater than the upper normal limit for AST and ALT in 11.1% and 7.4% of patients respectively [10].

Kularatne et al enrolled 404 patients in srilankamean duration of fever 7 days (range

1-19 days). Mean total white blood cell and platelet counts started to fall from the second day of fever, with the lowest counts on the 5th to 7th days. Packed cell volume (PCV) showed minimum fluctuation. One hundred and sixty (88%) patients showed elevated liver enzymes (ALT and AST), with 122 of them having a two-fold increase. Three patients died, and complications such as myocarditis, large effusions, encephalopathy, acute renal failure, acute liver failure and diarrhea were observed. These results suggest that a combination of clinical picture, thrombocytopenia, leukopenia and elevated liver enzymes could be used as markers for early diagnosis of dengue infection [11].

Dinh The Trung, et al Prospectively recruited 740 patients admitted in Infectious disease hospital in southern Vietnam, , liver involvement demonstrated by increases in transaminase levels occurred in almost all patients and correlated with disease severity in terms of vascular leakage and bleeding. Jaundice and acute liver failure developed in only a small proportion of patients and occurred relatively late in the disease course, usually without evidence of vascular leakage severe enough to cause shock. Severe bleeding was more frequent, but also occurred commonly in the absence of major vascular leakage [12].

Lum LC, et al. Eight cases of liver failure and encephalopathy were observed among twenty cases of grade and grade 4 (DHF/DSS) admitted to the department of pediatrics, University hospital, Kuala Lumpur from Jan 1990 to Dec 1991. All patients with deterioration in mental status showed a marked increase in liver enzymes (AST and ALT) [13].

Seneviratne SL, et al. The dengue virus can infect many cell types and cause diverse clinical and pathological effects. We describe clinical and experimental observations that suggest that liver involvement occurs during dengue infections, and we outline the possible role played by host immune responses in this process [14].

Amritharoy, et al. studied 120 patient admitted in eastern india concluded that Hepatic involvement in dengue varies from jaundice to more than 10-folds elevation of liver enzymes. Hepatomegaly is a most important clinical sign, but alteration of LFT's can occur with or without hepatomegaly. Significant rise of liver enzymes signifies severe dengue. Presence of fever, jaundice and hepatomegaly in endemic areas should arouse the suspicion of dengue hepatitis in addition to malaria, enteric fever and viral hepatitis [15].

Clinical Implication: The present study has a potentially important implication for clinicians in developing countries. SGOT/SGPT can be used as an economic test to diagnose patient with requirement of admission to intensive care unit. Transaminases might guide physician in their clinical decision and may provide step wise approach to management of dengue cases by serial measurement of their level.

Conclusions

Transaminitis is an important prognostic marker in Dengue fever and can be used early to distinguish between Dengue fever, Dengue hemorrhagic fever and Dengue shock syndrome at time of clinical presentation by looking at the severity of rise. Amongst the clinical spectrum observed it was observed that Dengue fever was a more common manifestation than DHF or DSS. The patients who presented late were seen to suffer from more severe form of the disease. The raise in SGOT and SGPT correlated inversely with fall in platelet count i.e. the more severe the Transaminitis, the more lower the platelet count. The raise of SGOT and SGPT correlated proportionately with the spectrum of disease severity.

Limitations of study: Transaminases level and platelet count collected on day of admission to hospital not during onset of symptoms. Presentation of patient to hospital from appearance of symptoms is different for each individual.

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