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Study of correlation between cardiac manifestations and deranged liver function test in patients in Dengue fever

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Abstract

Background: Dengue infection is an arthropod-borne infection that ranges from asymptomatic infection to severe cases of dengue shock syndrome. While myocardial involvement in dengue has been previously observed, the relationship between abnormal liver function tests and cardiac complications has not been established. This study was designed to address this issue.

Methods: A cross-sectional study was conducted on 100 patients hospitalised with dengue, confirmed by positive NS1 dengue infection and positive IgG and IgM antibodies. On the first day of admission, the patients underwent an ECG followed by liver function tests and evaluation of Creatine kinase-MB (CKMB). Radiographic techniques in the form of X-ray and Ultrasonography abdomen were employed in the study to evaluate severe conditions in the form of dengue shock syndrome presenting with ascites and pleural effusion.

Results: A total of one hundred patients were evaluated for the study, of which 28 of the patients showed clinically appreciable hepatomegaly. Of these 11 patients had manifestations of ascites and pleural effusion confirmation supplemented by auscultation and imaging studies. 12 patients presented with petechiae and bleeding through orifices of the 90 who had low platelet counts (below 100,000 micro-liters of blood).3 patients presented with bradycardia on monitoring their ECG and a rise in the CKMB levels was found in 26 patients.

Liver function tests showed an abnormality (raised SGOT/ SGPT levels above 40 U/L) in 99 patients, with 61patients had normal serum albumin levels. It was seen that out of 100 patients as a part of the study, 91 patients presented with values twice above the normal value for SGOT/SGPT, and 21 of the above 91 patients, along with a deranged liver function test, also had an elevated cardiac enzyme level(CKMB). This equates to 23.07% (21 of 91) of the patients having increased cardiac enzyme levels, compared to one out of eight (which equates to 12.5%) who had raised cardiac enzyme levels in slightly raised SGOT/SGPT levels, thus suggesting association between patients with dengue hepatitis and those having dengue myocarditis.

Conclusion: Patients having dengue hepatitis with twice the normal liver enzymes may be associated with dengue myocarditis. This association needs further research in view of pathophysiology and treatment

Keywords: Dengue, Cardiac Manifestations, Bradycardia, CKMB, Shock, Dengue Hepatitis.

Introduction

Dengue fever, a usually mild albeit debilitating viral fever (also known as breakbone fever) is commonly seen in the tropics where the urban-dwelling Aedes aegypti mosquito is the most common vector responsible for spreading the disease. A related mosquito, Aedes albopictus, is also commonly seen as a vector. Dengue is a rapidly emerging pandemic-prone viral disease in many parts of the world, most commonly affecting the tropical and subtropical regions. [1]

Dengue is caused by the Dengue virus (DENV) through the bite of an infected mosquito. While most cases are asymptomatic and produce only mild infections, some cases infected by DENV will progress to more severe cases and may even lead to death. Dengue fever is caused by four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, and DENV4) of the genus Flavivirus.

The transmission of DENV to human occurs through mosquito bite. This occurs 2 days before someone shows symptoms of the illness and up to 2 days after the fever has resolved. The presence of vertical transmission via maternal transfer (pregnant mother to fetus) is seen at a low rate, but the baby is seen to suffer from preterm birth, low birth weight and fetal distress. The global burden for dengue cases has increased from 505,450 in 2000 to 5.2 million in 2019. Most cases are asymptomatic or mild and self-managed; hence, dengue cases are underreported. Most of the cases are misdiagnosed as other febrile illnesses. [2]

Diagnosis of dengue is based on the results of dengue serological tests, which detect the presence of antibodies produced by the immune system against the virus. There are two types of antibodies produced by the body IgG and IgM. These tests are most effective when carried out 4 days after exposure to the virus. The presence of IgM or high IgG levels in the acute serum sample strongly suggests dengue infection. To confirm the presence of dengue infection, detecting dengue virus antigen NS1 antigen is the most sensitive and specific test. This test can be carried out 1-2 days after infection and is useful for early diagnosis. Additional tests, such as a complete blood count to monitor platelet counts and hematocrit levels, are important for managing the disease. A liver function test can also be carried out to check for elevated serum bilirubin levels and transaminase levels, which may indicate liver failure with fatal outcomes.

There is no specific treatment of dengue infection. Management is focused on symptomatic relief with

over-the-counter medicine such as paracetamol given to manage fever and muscle pain. Hypovolemia is managed by oral rehydration of fluids. The administration of fluids depends on hematocrit levels. In cases of severe dengue, immediate hospital admission is necessary for supportive care, intravenous fluid administration, electrolyte replacement blood pressure monitoring and transfusion to replace blood loss [3]

Liver involvement in dengue is usually manifested by hepatomegaly (clinically) or increase in liver enzymes (biochemically). Presentation with jaundice can simulate acute hepatitis. Severe dengue can manifest with fulminant hepatic failure [5].

It has been suggested that Ventricular arrhythmia, Atrial fibrillation and atrio-ventricular block are primarily observed during the acute stages of dengue infection. In the convalescent stage of dengue, most reported cardiac rhythm abnormalities are bradyarrhythmia or premature atrial and/or ventricular beats [4]. Dengue infection causes structural and functional changes in the heart, as documented in some 2D ECHO reports. These cases can range from self-limiting arrhythmia to severe myocardial infarction, myocarditis, pericarditis leading to hypotension, pulmonary oedema and cardiogenic shock[6].

Cardiac manifestations leading to functional myocardial deterioration in dengue cases have been described by some authors but are often under diagnosed in clinical practice. These cardiovascular manifestations are most commonly seen in the haemorrhagic form or in the cases associated with shock[6].

There is liver involvement in dengue fever and there is cardiac involvement i.e myocarditis in dengue fever. This study aims to find whether any association exists between dengue hepatitis (jaundice and elevated liver enzymes) and myocarditis (bradycardia and elevated CKMB). The study also aims to monitor cardiac manifestations in patients with dengue fever and identify subclinical/latent cardiac involvement in dengue cases with associated derangement in liver function.

Materials and Methods

The assessment tool used for this cross-sectional study was the STROBE checklist.

This study is a descriptive study conducted over a 6-month period, involving 100 patients. It was carried out in the Department of Medicine at Dr D.Y. Patil Medical College, Hospital & Research Centre Pune. The study focused on patients who presented to the hospital with dengue fever between January 2023 and June 2023. the inclusion criteria for the study were patients over 18 years of age who tested positive for one of the following or both: Dengue NS1 antigen, Dengue IgM. Patients with mixed infections, ECG suggestive of old myocardial infarction, any history of cardiac illness, or ongoing medications that affect heart rate were excluded from the study.

Ethical clearance was obtained prior to the start of the study (EC/RENEW/INST/2019/6302), and written informed consent was obtained from all participating patients. All patients underwent a general physical and systemic examination, as well as a series of tests including:

Hemogram: to evaluate platelet count and hematocrit levels, as hematocrit levels greater than 20% indicate hemoconcentration and precede shock.

ECG: ECG was done immediately on day of admission to identify common ECG findings such as sinus bradycardia, as well as less common findings like ventricular premature beats, atrioventricular dissociation, and ventricular tachycardia. ECG with QS complexes, broad QRS, LBBB pattern were considered to have prior

myocardial damage and were excluded.

- USG (abdomen and pelvis): to detect ascites, a common manifestation of severe dengue due to vascular leakage. Abdominal ultrasound is the recommended imaging method for studying ascites. Ultrasound Abdomen was done on day 2 of admission. In ultrasonography abdomen, the length of right liver lobe >16.5 cm was considered as hepatomegaly. Ultrasonography abdomen was done by single observer.

- Liver function test: to assess transaminitis, hypoalbuminemia, and reversal of A:G ratio, which are biochemical markers used to detect and monitor hepatic dysfunction in dengue patients.

PT/INR: To identify bleeding manifestations.

Chest X-Ray: To look for signs of pleural effusion, which is commonly seen in cases of shock.

Cardiac Enzymes: CKMB [CKMB levels 0-25IU were considered normal. Above 25 IU were considered raised] Rapid Dengue test (NS1 antigen, IgG, IgM)Dengue [NS1 antigen by(J Mitra Dengue card Test), Dengue IgM and IgG by ELISA method]

ECG was performed on the day of admission, cardiac enzyme tests were conducted on day one, and liver function tests were also carried out on the same day. CKMB values outside the range of 0-25IU were considered deranged. Similarly, patients with serum bilirubin levels above 1mg/dl, AST levels above 8-48U/L, or ALT levels above 7-55U/L were considered to have deranged liver function tests.

Dengue patients who tested positive for one of the aforementioned investigations, with or without clinical features, were considered positive for cardiac manifestations and deranged liver function tests. Cardiac manifestations included rhythm disturbances, heart rate changes (such as sinus tachycardia or bradycardia), and raised CKMB levels with an abnormal ECG.

The study also included radiographic interpretation of chest X-rays. Patients with pleural effusion, defined as abnormal fluid accumulation in the pleural cavity, were considered important in the statistical analysis. Pleural effusion indicates plasma leakage in cases of dengue and suggests the severity of the infection.

Furthermore, USG abdomen studies were conducted which identified hepatomegaly and ascites in some patients.

EXCEL sheets and SPSS software were used for statistical analysis.

Results

The study included 100 patients, with 54 being male (54%) and 46 being female (46%). The average age for female patients was 33.67 years, while for male patients it was 30.68 years.

The most common clinical presentation was fever, observed in 98 patients, followed by myalgia in 85 patients, abdominal pain in 67 patients, retro-orbital pain in 77 patients, and headache in 80 patients.

Amongst a constellation of clinical signs, 28% (28 of 100) of the patients showed clinically appreciable Hepatomegaly (Figure 1).

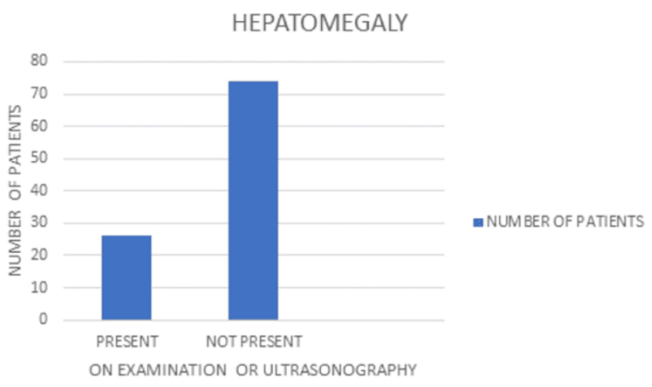

Figure 1: Incidence of hepatomegaly in the study

Almost 11% (n=11) of the patients showed signs suggestive of Ascites and pleural effusion where bilateral basal crepitations were observed on auscultation which was confirmed later in imaging studies (Figure 2)

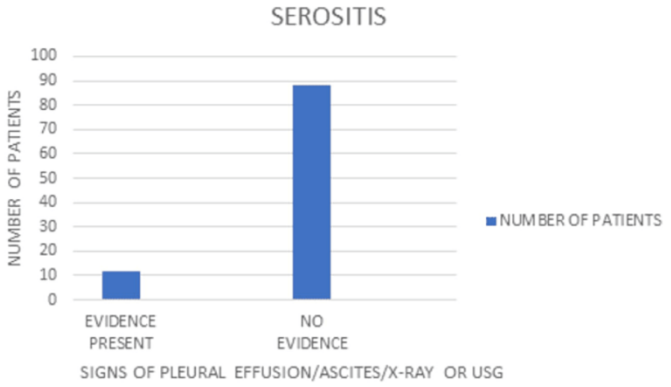

Figure 2: Signs of Pleural effusion/ Ascites on x-ray or USG

While 12% (n=12) presented with signs of bleeding tendencies clinically (rash/bleeding through orifices), as seen in (Figure 3) where 12% (n=12) of the patients have platelet counts below 100,000 per micro-liter of blood.

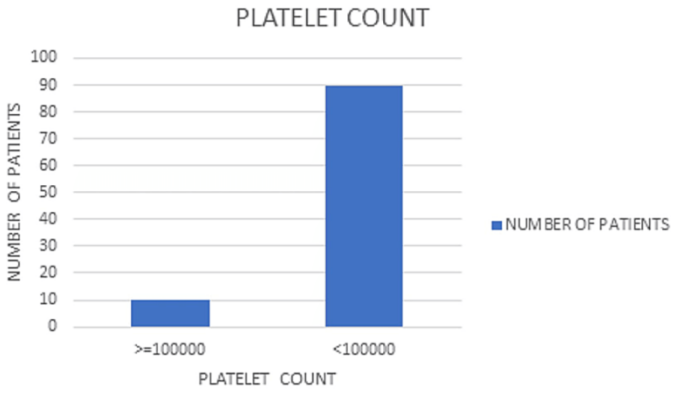

Figure 3: Platelet count in the study group

Grading the severity of dengue infection was made based on signs of shock in the patients, which included- Tachycardia (heart rate >100/min), narrow pulse pressure (<30mm Hg), low blood pressure, tachypnea (respiratory rate >20 cycles/ min) and presence of cold peripheries.

On admission of the patients for dengue, out of 100 patients, 97% (n=97) of patients presented an ECG in normal sinus rhythm (Figure 4), while 3% (n=3) presented with bradycardia (heart rate < 60/min).

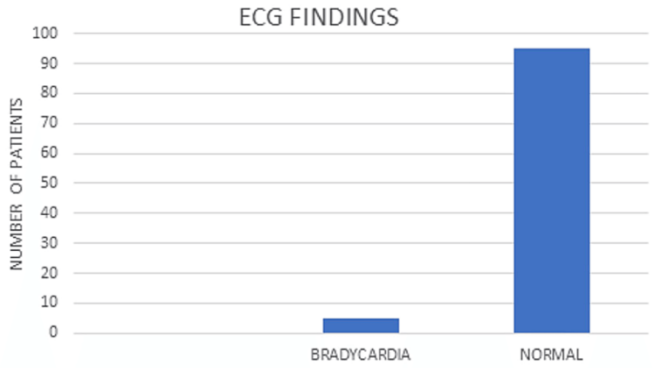

Figure 4: ECG findings in the study group

In the present study, 26% (n=26) of the patients presented with raised CK-MB (Figure 5.), while the remaining 74% (n=74) had cardiac enzymes within the normal range.

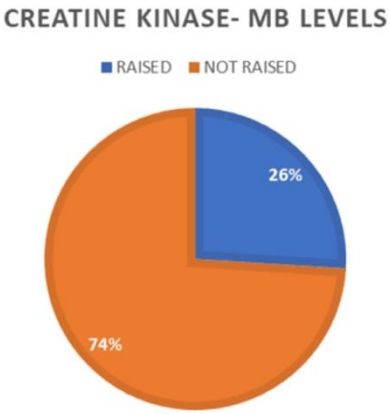

Figure 5: CKMB levels in the study group

When liver function tests were carried out, 99% of patients presented with a deranged liver function test; further investigation found that 61 %(n=61) of the patients were measured for a normal serum albumin level (>=3.5mg/dl), as seen in (Figure 6).

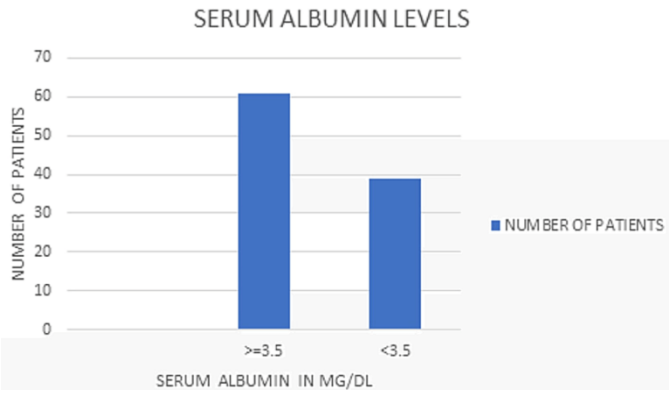

Figure 6: Serum Albumin levels in mg/dl

Out of the 100 patients in the study, 6% were reported to have Dengue shock syndrome, 12% were diagnosed with Dengue Hemorrhagic fever, and the remaining 82% were reported to have Dengue fever.

	No. of patients	Patients with raised CKMB
AST> 80mg/dl (single)	89	25
ALT> 80mg/dl (single)	70	24
AST & ALT> 80mg/dl	70	24

Table 1: Data for patients with deranged liver function test and elevated CKMB

It was seen in the study that 99 patients presented with deranged liver function tests and only one patient returned with a normal result for the liver function test (Figure 7).

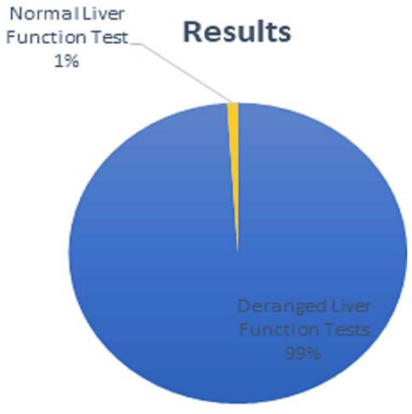

Figure 7: Results for patients with deranged liver function test

ECG and CKMB evaluations were essential for assessing cardiac dysfunction. Two patients showed abnormalities in the ECG, specifically sinus tachycardia, as well as abnormal CKMB and liver function test results. On the other hand, three patients had bradycardia and abnormal levels of CKMB and transaminase enzymes. The study revealed that 21 patients had elevated CKMB levels, deranged liver function tests, and no other abnormalities.

Out of the 100 patients in the study, 91 had AST/ALT levels that were more than two times higher than normal. 8 patients had slightly elevated AST/ALT. 1 patient had normal AST/ALT. Among these 91 patients who had twice normal AST/ALT, 21 had both deranged liver function tests and elevated cardiac enzyme levels, i.e 23.07% of those with severe hepatitis also had cardiac involvement. In contrast, only 1 out of 8 patients (12.5%) with slightly increased AST/ALT levels had elevated cardiac enzyme levels.

Discussion

Dengue is a viral illness that is becoming more prevalent and has serious consequences, particularly in developing countries. It has had a significant impact on healthcare systems worldwide. While there are many cases of dengue infection, there is limited published data on cardiac manifestations in these patients. The objective of this study was to find a relationship between myocardial alterations and liver function tests in patients with dengue fever.

This observational study involved 100 patients, with 54 being male and 46 being female. A similar study by Neelakanth S Patil et al. included 1111 patients, with 656 (59.05%) being male and 455 (40.95%) being female [5]. The average age of the patients in our study was 33.67 years, with the majority falling between 20-35

years old. The lifestyle habits of this relatively young population, such as not properly covering their extremities or using mosquito nets or repellents while sleeping outdoors, may contribute to the higher number of cases in this age group. In our study, 98% of the patients reported fever, compared to 81% in a study by Carlos Henrique Miranda et al. additionally, 80.56% and 81.35% of our patients reported myalgia and headache, respectively, compared to 85% and 80% in the same study [6].

In our study, 81% of the patients had platelet counts between 20,000 and 99,000. 9% had platelet counts below 20,000, and 10% had counts over 100,000. This is similar to a study by Amitava Acharya et al., where 36.9% had platelet counts between 36,000-100,000 and 10.5% had counts below 35,000 [7].

We also found that 11% of the patients showed signs of ascites and pleural effusion, with bilateral pleural effusion observed on auscultation. This is consistent with a study by Suhendro Suwarto, where 58.7% of dengue patients showed pleural effusion and ascites [8].

On examination of the liver, 28% of the patients showed clinically appreciable jaundice. This differs from a study by Jayanta Samantha, which showed hepatomegaly in 4-52% of adult dengue patients [9].

Hepatic involvement was determined based on elevated hepatic transaminase levels. In our study, 99 patients showed elevations in serum AST and ALT levels, compared to 74.88% in the previous study. The hepatic damage seen in these cases may be due to the direct effects of the virus, immune responses against the virus, or viral serotypes targeting liver tissue.

ECG was found to be a sensitive method for diagnosing myocarditis in patients. Of the dengue patients admitted, 97% had a normal sinus rhythm on the ECG, while 3% showed abnormal rhythms, typically bradycardia. None of the patients had abnormal echocardiography. 24 patients showed raised CKMB and a biphasic rise in AST/ALT levels, contrasting with a study by Yingying Li et al., where 76.12% of patients had abnormal ECG results [10].

In our study, 91 patients had AST/ALT levels raised more than two times, and 21 of those patients had deranged liver function tests and raised cardiac enzyme levels. This equates to 23.07% of the database having increased cardiac enzyme levels. This differs from a study by Carlos Henrique Miranda et al., which reported a 15% rate of cardiac abnormalities in dengue patients [6].

Cardiac dysfunction in the acute phase of dengue fever is often under diagnosed. While specific cardiac manifestations are rare, myocardial depression associated with deranged liver function tests is common in dengue hemorrhagic fever and dengue shock syndrome. Proper management is needed to address the hemodynamic instability and ventricular dysfunction. Recent studies have suggested that cardiac involvement may contribute to shock in dengue hemorrhagic fever.

Dengue hemorrhagic fever is an immunologically mediated disease, similar to viral myocarditis, which may play a role in the development of dengue virus-related myocarditis. These cases are often under diagnosed, leading to increased mortality. This highlights the need for improved management strategies.

Limitations of this study include the inability to perform cardiac biopsies, which are considered the gold standard for diagnosing myocarditis. Central venous pressure was not measured, and there was no correlation between CVP and cardiac involvement. A larger sample size could have provided more diverse patients. Additionally,

the study did not effectively grade patients based on severity into dengue fever, dengue hemorrhagic fever, and dengue shock syndrome.

Conclusions

In conclusion, this study highlights the clinical and diagnostic characteristics of dengue myocarditis and its association with abnormal liver function tests in different levels of disease severity. The most noticeable clinical manifestations are rhythm abnormalities, which can be life-threatening and lead to shock and death. It is crucial for healthcare professionals to closely monitor cases of myocarditis to minimize complications. Fortunately, these complications are usually temporary, and the development of severe dilated cardiomyopathy is rare[10]. Clinicians must be aware of the epidemiological risk factors and symptoms suggestive of cardiac involvement to take appropriate measures and prevent the disease from progressing to more severe forms.

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