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RESEARCH ARTICLE

SERUM TRANSAMINASES AND CALCIUM LEVELS IN PATIENTS WITH DENGUE FEVER: A HOSPITAL BASED STUDY

¹Ashok Kumar Shah, ^{2*}Arpita Suri, ³Birendra Kumar Yadav, ⁴Nisha Chauhan, ⁵Sanjiv Kumar Bansal, ⁶Busi Karunanand

¹Assistant Professor, Department of Biochemistry, World College of Medical Sciences & Research, Jhajjar, Haryana, India

^{2*}Assistant Professor, Department of Biochemistry, SGT Medical College, Hospital & Research Institute, Gurugram, Haryana, India

^{3,4}Tutor, Department of Biochemistry, SGT Medical College, Hospital & Research Institute, Gurugram, Haryana, India

⁵Professor, Department of Biochemistry, SGT Medical College, Hospital & Research Institute, Gurugram, Haryana, India

⁶Professor & Head, Department of Biochemistry, SGT Medical College, Hospital & Research Institute, Gurugram, Haryana, India

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ABSTRACT

Background & Objectives: Dengue fever is associated with significant morbidity and mortality there by initiation of timely management of the patient to prevent complications is the need of the time. Our study focuses on biochemical alterations associated with dengue fever which would help in early identification and management of patients. **Materials & Methods:** In this case-control study, clinically diagnosed patients of dengue (n=50) and age-matched healthy controls (n=50) were enrolled. Serum bilirubin, transaminases and calcium levels were estimated in both the groups and further compared using Independent student's t-test. **Results:** The mean level of serum bilirubin in patients with dengue fever were significantly higher ($p<0.01$) than controls. The mean serum levels of both the liver enzymes, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were significantly increased ($p<0.000$) whereas the mean serum calcium level of dengue patients was significantly decreased ($p<0.000$) than the healthy controls. **Interpretation & Conclusion:** Dengue fever is characterized by various biochemical attentions such as increased transaminases, raised bilirubin and low calcium. These investigations will help in early identification, diagnosis and management of dengue patients.

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INTRODUCTION

Dengue is an arthropod-borne viral disease transmitted by single stranded RNA virus belonging to Flaviviridae family. It is transmitted by bite of *Aedes aegypti* mosquito (Platt et al., 1997). The virus can belong to closely related but serologically distinct serotypes DEN-1, DEN-2, DEN-3 and DEN-4 (Nimmannithya, 2009). Recent estimate in 2013 indicated 390-million dengue infections every year of which 96 million manifest clinically. 3.9 billion People in 128 countries are at risk of infection with dengue viruses (Bhatt et al., 2013).

*Corresponding author: Arpita Suri,
Department of Biochemistry, SGT Medical College, Hospital & Research Institute, Gurugram, Haryana, India.

Every year 50 to 100 million infection of Dengue fever occur with case fatality rate of around 5%. The numbers of cases of dengue are increasing due to its spread to new areas and more out breaks are occurring worldwide. In 2015, Delhi, India recorded its worst outbreak since 2006 with over 15,000 cases (Neeraja et al., 2013). The pathogenesis of dengue fever is multifactorial. The virus causes activation of endothelial cells. The virus is associated with infecting WBC and thereby secretion from cytokines occurs, which causes flu like symptoms. The fluid leakage due to capillary permeability is responsible for less blood supply to organs. Dysfunction of bone marrow causes decrease in number of platelets that leads to complication of dengue fever like hemorrhages. In complicated form, there is enhanced formation of immune

complex due to immune response towards virus (Srichaikul, 2000). This further leads to complement activation and release of cytokines leading to coagulation abnormalities and DIC. Dengue is a disease with various clinical presentations varying from asymptomatic to flu like state (DF) to severe form with various complications (DSS or DHF) (Brasil 2005). Dengue is characterized by sudden onset of fever, headache (behind the eyes), muscle and joint pains and rash. Primary abnormality is acute increase in vascular permeability leading to hemoconcentration and decreased Blood Pressure (Gubler, 1998). Dengue is diagnosed mainly clinically based on clinical symptoms and physical examination. Earliest changes include low white blood cell count followed by low platelets. We plan to study various other biochemical changes also with dengue infection. Dengue fever is associated with neutropenia followed by lymphocytosis (Laboratory diagnosis of dengue virus infection, 2005). Due to its significant morbidity and mortality in tropical areas, lot of research is being focused on dengue. The aim of the present study is to evaluate the biochemical changes in dengue patients and compare with the healthy controls.

MATERIALS & METHODS

The present study was conducted in the Department of Biochemistry, S.G.T. Medical College, Hospital & Research Institute, Gurugram, Delhi-NCR. Fifty (50) samples of inpatient wards were taken with confirmed dengue infection and 50 age and sex matched normal healthy controls were recruited for the study after written informed consent was obtained. The confirmed dengue patients had positive acute dengue serology, detected by Dengue Duo IgM & IgG Rapid Strip Test (J. Mitra & Co. PVT. LTD.) and fulfilled clinical diagnostic criteria of dengue fever by WHO (1997).

Inclusion Criteria: Patients with the confirmatory diagnosis of dengue.

Exclusion Criteria: patients with;

- Hypertension
- Diabetes and Cardiac diseases
- Those on anti-hypertension/anti-arrhythmic medications
- Malaria and Filariasis
- Calcium supplements
- Any drugs affecting calcium homeostasis,

Ethical approval for the study was obtained from the Institutional Ethical Committee (IEC), Faculty of Medicine & Health Sciences, S.G.T. University, Gurugram, Delhi-NCR, India.

Biochemical Investigations: About 5 ml of venous blood samples were collected in the red-capped (plain) vacutainer. The sample was allowed to clot & centrifuged at 3000 rpm for 10 minutes and serum was separated. Estimation of serum calcium, Liver Function Tests (LFT) and Renal Function Tests (RFT) were assayed by using commercial kits available for standard spectrophotometric methods in fully automated ERBA XL (EM-200) and BS-300 Biochemistry analyzers after ensuring about the quality control of the respective parameters.

Statistical Analysis: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 for windows (SPSS, Inc., Chicago). The quantitative data were expressed as mean \pm standard deviation (SD).

Independent Student's t-test was used to compare the mean serum level of all the parameters between cases and controls. $p < 0.05$ was considered statistically significant.

RESULTS

Demographic features: Among the 50 patients diagnosed with dengue, 27 were males and 23 were females. Their age ranges from 4 years to 60 years with a mean age of 24.38 years.

Biochemical profile: We have evaluated both the dengue patients and the control subjects for Serum Bilirubin, liver enzymes; Aspartate Aminotransferase (AST) & Alanine Aminotransferase (ALT) and serum Calcium levels. Comparisons were made between both the groups and the result was shown in the Table 2.

Table 1. Age distribution of patients with dengue fever (n = 50)

Age groups (years)	Number of cases
0-10	6
11-20	14
21-30	18
31-40	7
41-50	3
>50	2
Total	50

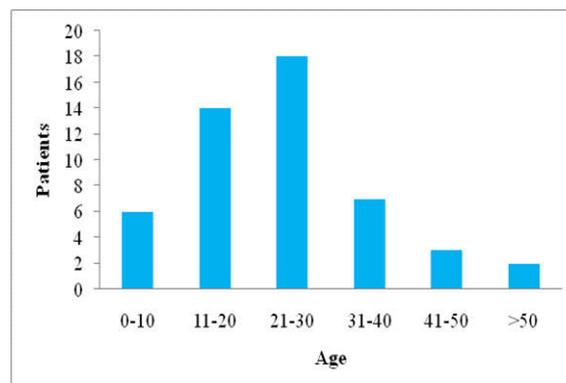


Figure 1. Age distribution of patients with dengue fever

Table 2. Comparison of Biochemical measurements among Dengue subjects and controls

Parameters	Dengue cases Mean \pm SD	Controls Mean \pm SD	p-value
Serum Bilirubin (mg/dL)	0.86 \pm 0.49	0.63 \pm 0.30	0.005
AST (IU/L)	53.43 \pm 32.51	24.80 \pm 9.31	0.000
ALT (IU/L)	38.63 \pm 24.29	21.80 \pm 6.40	0.000
Calcium (mg/dL)	6.85 \pm 1.68	9.24 \pm 0.66	0.000

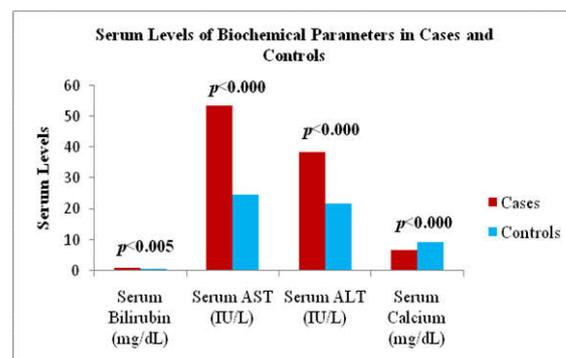


Figure 2. Comparison of Biochemical measurements among Dengue subjects and controls

The mean level of serum bilirubin in the patients with dengue fever were significantly higher ($p < 0.005$) than controls. The mean serum levels of both the liver enzymes, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were significantly increased in dengue patients ($p < 0.000$) compared to the control subjects. The mean serum calcium level of dengue patients were significantly decreased ($p < 0.000$) than the healthy controls.

DISCUSSION

The mean level of serum bilirubin in cases was higher than in controls (0.86 ± 0.49 mg/dL, $p < 0.005$). Patel *et al.* (2016) also reported in their study that serum bilirubin was raised in 4% of patients. Yaseen *et al.* (2017) who did the study on 100 seropositive dengue cases and reported raised bilirubin in 4% of cases. Tahlan *et al.* (2017) also observed mild hyperbilirubinemia in 14.28% of the cases. In contrast, Nazish Butt *et al.* (2008) who did the study on 104 patients and found only abnormality in AST & ALT with respect to liver function test. It can be associated with liver involvement due to hypoxia caused by dengue infection. The level of ALT was significantly increased ($p < 0.000$) in cases (38.63 ± 24.29 IU/L) as compared to controls (21.80 ± 6.40 IU/L). In 2012, Raimuda *et al.* did similar retrospective study on 154 patients who tested positive for dengue serology and found elevated transaminases (ALT and AST). Ramandeep *et al.* (2014) in 2014 also found increase in transaminases in dengue patients. In 2016, PM Patel *et al.* (2016) did a study on 250 dengue patients and found increased ALT in 40% of dengue patients. In addition, in 2017, Tahlan, (2017) found increased transaminases (AST & ALT) in 47.61% dengue patients. In 2015, Ravi Shankar *et al.* (2017) compared levels of transaminases between three groups of dengue patients from 1 month to children ≤ 18 years and found significant increase in dengue patients more so in group with warning signs. They concluded that 4-fold elevation within 96 hours of onset of symptoms was a reliable predictor of severity of dengue. In 2007, Souza (2007) postulated that due to involvement of liver in dengue, there is rise in transaminases.

There is hypoxic injury to hepatocytes leads to leakage of intracellular transaminases (ALT & AST). In our study, level of calcium was lower in cases as compared to controls and the difference was significant. Dahanayaka *et al.* (2017) in 2017 did a study on 36 patients of Dengue fever and found 17 (54.8%) of cases either had hypocalcemia in admission or during hospital stay and those patients with hypocalcemia (low serum ionized calcium) had lower platelet and albumin level with significant p value. In 2015, Habbu PP *et al.* found low calcium value in Dengue subjects as compared to healthy controls. Few studies have associated hypocalcemia with disease severity. Constantine *et al.* also suggested association of hypocalcemia with disease severity in patients with dengue being more prevalent in DHF (Dengue Hemorrhagic Fever). Zaloga GP *et al.* (1987) postulated that several causes of hypocalcemia might be there including Na^+ K^+ ATPase activity, Ca^{2+} ATPase, acquired parathyroid deficiency, α' hydroxylase insufficiency, and decreased vitamin-D intake. It has been suggested by Chaturvedi *et al.* that Ca^{2+} induces dengue specific T-helper cells and dengue antigen increases the influx of calcium into T-cells, which can be responsible for hypocalcemia. Few interventional studies, which include administration of oral calcium carbonate to dengue patients, have obscured a significant increase in platelet count and

clinical features improving (Sanchez-Valdez *et al.*, Cabrera-Cortina *et al.*). However, the limited evidence suggests that more number of interventional studies is required to confirm its benefit. There are various limitations in our study. In our study serum, total calcium was used to indicate hypocalcemia instead of ionized free calcium, which is better indicator of calcium status of the body. Moreover, we have not further segregated dengue patients into DF or patients with DSS or DHF to compare degree of hypocalcemia or rise in transaminases with severity of disease. Lastly, we have not evaluated the days from the onset of the symptoms when the particular parameter was raised.

CONCLUSION

Dengue fever is characterized by various biochemical attentions such as increased transaminases, raised bilirubin and low calcium. These investigations will help in early identification, diagnosis and management of dengue patients. This would further enable to reduce morbidity and mortality associated with the disease and it would help to initiate timely management of patient to prevent complications associated with dengue. However, there is limited evidence whether oral administration of calcium improves the clinical status of patient. Hence, more of interventional studies are required to validate the beneficial action of oral calcium supplement in decreasing the progression of dengue fever.

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