

Original article

Impact of dengue on liver dysfunction in Children

Dr.Renuka S Jadhav, Dr.Maya Borle, Dr.SR Agarkhedkar, Dr.Sagar Bhalani

Name of the Institute/college: Department of Pediatrics, Dr.DY Patil Medical College, Hospital and Research Centre, Pimpri, Pune

Corresponding author: Dr.Maya Borle

Abstract:

Introduction: Dengue is an important arboviral infection in the world.DSS (Dengue Shock Syndrome) and DHF(Dengue Hemorrhagic Fever) have emerged as major public health problems of International concern. This study was designed to find the role of Liver involvement and liver function tests in predicting Severe forms of Dengue.

Material and Methods: A Cross-sectional prospective study was undertaken in a tertiary hospital in Pimpri, Pune. Patients were divided into two groups Severe Dengue which included Dengue Hemorrhagic Fever and Dengue Shock Syndrome, and Dengue Fever(DF) without complications. Detailed history, examination and relevant investigations were done.

Results: Dengue showed seasonal trend with maximum cases in October to November. Serum AST(Aspartate Aminotransferases) and ALT(Alanine Aminotransferases) were significantly increased in severe dengue.AST levels were higher. Prolonged PT(Prothrombin time) was associated with severity of infection and bleeding.

Conclusion: AST,ALT,PT can serve as predictors of severe forms of Dengue thus helping in appropriate and timely intervention, thereby preventing potential mortality.

Keywords: Dengue, Hepatitis, Aspartate aminotransferases, Alanine Aminotransferases

Introduction:

Dengue is an important health problem worldwide.¹ Dengue virus is a Flavivirus transmitted by *Aedes aegypti* mosquito. Many different types of clinical manifestations of Dengue Infection have emerged in past few years. This has been creating major problem in early detection of Dengue fever. Classically WHO divides Dengue into three categories:1)Dengue Fever 2)Dengue Fever with warning signs 3)Severe Dengue. The illness is characterized by biphasic fever which may be accompanied by hemorrhagic manifestations and shock due to plasma leakage into third space. Simple dengue fever is characterized by fever, body ache, Sore throat, conjunctivitis and retro-orbital pain. Respiratory distress due to pleural

transudates or effusion and neurological involvement may also occur, the incubation period being 4 to 7 days. Due to these myriads of manifestations of a single virus it is difficult initially diagnose, then predict which cases will enter the critical phase and which cases will recover fast without complications.

Hepatomegaly, tender hepatomegaly and rarely icterus are manifestations of liver involvement. Along with these signs biochemical changes in form of elevated aminotransferases have been observed.

Clinical features indicating hepatic infection include symptoms of pain abdomen, loss of appetite, nausea and vomiting.^{2,3} Tender hepatomegaly leading to pain abdomen, and loss of appetite are seen more in severe Dengue (DSS and DHF) than in Dengue Fever. Liver

enlargement is seen commoner in severe type Dengue ,though it may be present in Dengue Fever.⁴

Four to fifty two percent of adult patients have been seen to have hepatic enlargement. However, clinically icterus is seen in 1.7 to 17% of the patients. Related to this the ,usual biochemical abnormality found is raised aminotransferases levels. AST levels have been found to be increased in 63%-97% of patients, while increased ALT levels are seen in 45%-96%. Many of the Dengue studies have shown that AST levels are increased more than compared to ALT. The trend is rising levels in first seven days of infection ,with a likelihood diminish to normal levels in 21 days time.⁵ The reason Of AST rising more than ALT could be release from the destroyed myocytes in the initial Dengue infection phase.⁶

DHF and DSS have been seen to have increased AST and ALT levels significantly more than the non severe form.^{7,8} It has also been noted that the value of Aminotransferases are raised more in acute febrile stage.

This discrepancy in the measure of AST/ALT ratio is not generally seen in the common Viral hepatitis due to Virus Hepatitis A,B or C. Thus this investigation can indicate the etiological factor only by looking at the Aminotransferases levels.

Thus this study was designed to diagnose Dengue hepatitis and predict the impending complications with help of biochemical parameters.

Materials and Methods:

Type of Study: : Prospective cross sectional study from July 2011 to September 2012.

Place of Study: Tertiary care center at semi urban area of Pimri ,Pune

Sample size: 80 patients-40 of 40 of Dengue fever and 40 with severe Dengue.

Institutional ethical clearance was obtained prior to starting of study.

Inclusion Criteria:

All children 1 year to 12 years of age who tested positive for dengue fever, Dengue hemorrhagic fever and dengue shock syndrome.

Exclusion Criteria: Those children who had known hematological disorder and those whose consent could not be obtained were excluded from study.

Methods:

Patients were divided into two groups-Severe Dengue Group having shock (DSS) or bleeding manifestations(DHF) and Dengue fever(DF) group without any complications.

Tourniquet test was done on each patient in addition to though physical examination.

NS1Ag, Dengue IgM, IgG test was carried out in every patient.

Other investigations of complete blood count, hematocrit, Platelet count, Aspartate aminotransferases (AST), Alanine Aminotransferases(ALT), Prothrombin time(PT), PTTK were done.

Evaluation:

Analysis was done using SPSS version 7 by applying chi square test, Odds ratio and Z test.

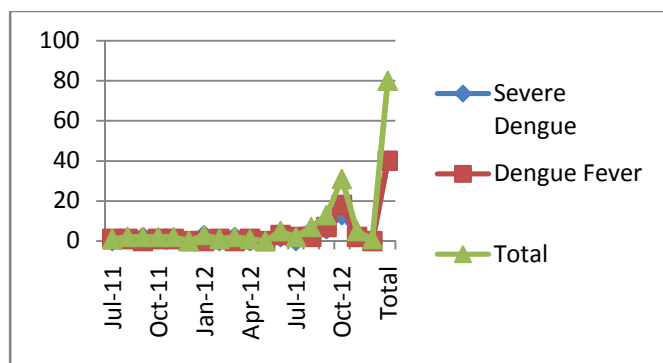
3. Results:

Table3.1 Monthly Distribution of cases in study groups:

Month/Year	Severe Dengue n=40	Dengue Fever n=40	Total N=80
July2011	0	1	1
Aug2011	1	1	2
Sep2011	2	0	2
Oct2011	1	1	2
Nov2011	1	1	2
Dec2011	0	0	0
Jan2012	3	0	3
Feb2012	0	1	1
Mar2012	2	0	2
Apr 2012	0	1	1
May2012	0	0	0
Jun2012	2	3	5
July2012	0	2	2
Aug2012	5	2	7
Sep2012	6	7	13
Oct2012	13	18	31
Nov2012	3	2	5
Dec2012	1	0	1
Total	40	40	80

Figure I

Line Diagram:monthly distribution of cases



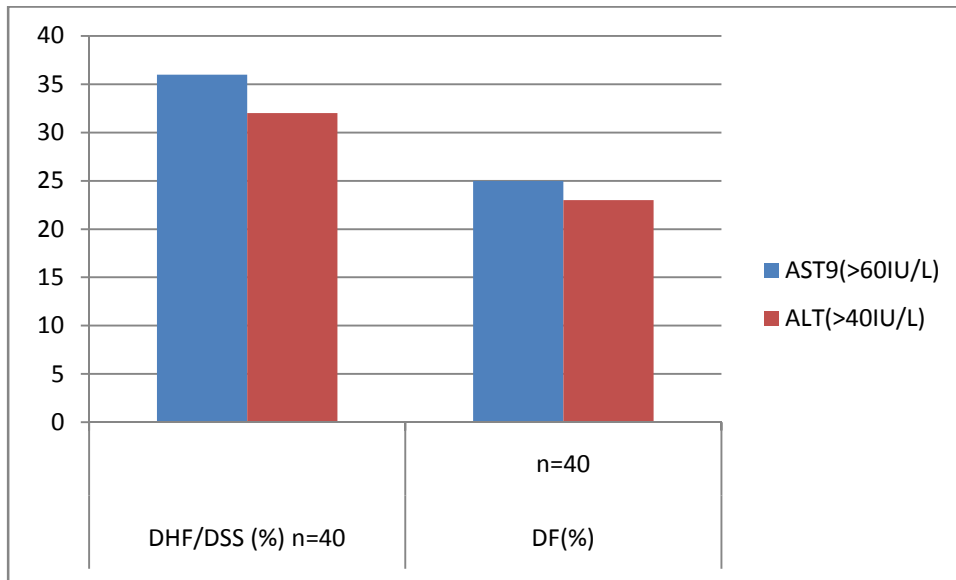
X axis shows number of cases.

Table 3.2 Comparison of Liver Enzymes in study group:

Liver enzyme	DHF/DSS (%) n=40	DF(%) n=40	Chi -Square	P Value
AST9(>60IU/L)	36	25	8.35	<0.0001
ALT(>40IU/L)	32	23	4.71	<0.05

Figure II

Bar Diagram: Liver Enzymes distribution in study group:



X-Axis :Enzymes levels in IU/L

AST: Sensitivity=90% Specificity=37.50% PPV=50.02% NPV=78.95% OR=5.4

ALT: Sensitivity=80% Specificity=42.50% PPV=58.18% NPV=68% OR=2.96

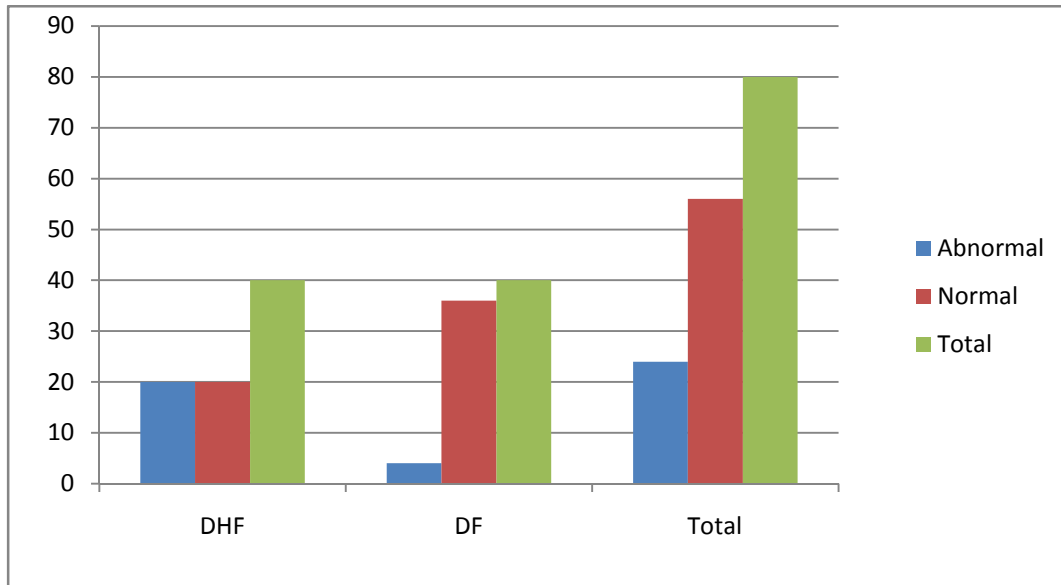
Table3.3 Prothrombin time(PT) wise distribution of cases in the study group:

PT	DHF	DF	Total
Abnormal	20	4	24
Normal	20	36	56
Total	40	40	80

Chi-Square=15.24 P Value=<0.0001 Sensitivity=50% Specificity=90% PPV=83.3% NPV=64.29%
OR=9

Figure III

Bar chart : Prothrombin time (PT) wise distribution of cases in the study group:



X-Axis :Enzymes levels in IU/L

Table 3.4 Comparison of Hepatomegaly and tender hepatomegaly in study groups

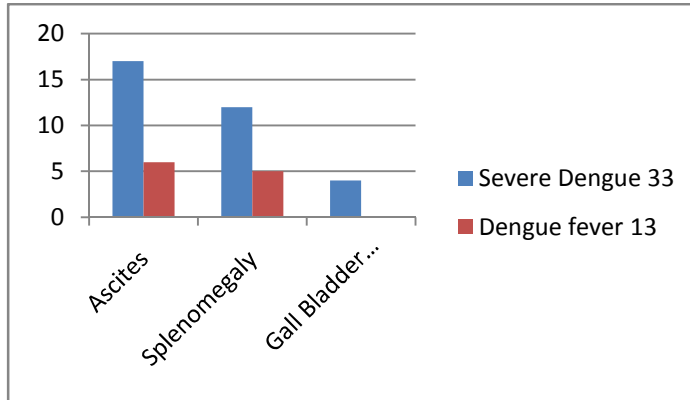
Parameter	Severe Dengue n=40	Dengue Fever n=40	Z value	P value
Hepatomegaly	35(87.50)	26(65)	2.45	<0.05
Tender Hepatomegaly	32(80)	14(35)	4.57	<0.0001

Hepatomegaly: Sensitivity=87.5%,Specificity=35%,OR=3.77

Tender Hepatomegaly: Sensitivity=80%,Specificity=65%,OR=7.43

Figure IV

Bar diagram showing pattern of hepatomegaly in study group



X Axis shows liver span in centimetres

Discussion:

The study conducted by us is in concurrence with other studies done in the developing countries, with reference to universal Liver involvement in Dengue infection. In this study ,maximum number of cases (44 cases ,55%)were seen in September and October 2012.Peaks of cases between August to November have been reported from India in SEA Update. The seasonal variation is a result of complex environmental influences like rain, humidity, temperature and movement of mosquitoes.An important laboratory finding we saw in our study was increased serum levels of both AST and ALT. Both were increased in DHF,DSS and Dengue fever.36(90%) patients od DHF and 25(31%) patients of Dengue fever showed raised AST(>60IU/L)which significant (P Value<0.001).32(80%) patients of DHF had raised ALT which was statistically significant. In a study by GN Malvige ,PK Ranatunge et al at Sri Lanka reported over50% children with abnormal Transaminases.⁹

The AST level were more than ALT levels.Kuo et al reported abnormal AST in 93.3% and ALT in 82.2

% .Mohan et al found abnormal Transaminases in96% while Souza et al showed altered AST and ALT in63.4% and 45% respectively.¹⁰

The study by Wong et al showed increased Alanine and Aspartate amino transferases in 91% and 72% respectively.¹¹ Wahid et al found serum AST and ALT levels to be significantly higher in patients with Severe dengue.M Narayanan observed 70% raised ALT levels signifying severe damage to liver.¹²

The AST/ALT ratio may prove to be useful in differentiating Hepatitis due to non dengue viral infection. AST levels are much higher in Dengue than ALT due to injury to muscles. Since the epidemics of viral hepatitis and Dengue tend to occur during same period of the year ,it will useful to compare the levels of AST versus ALT. Histopathologically ,the liver shows Kupffer cell hyperplasia,centrilobular necrosis and infiltration of portal tract with monocytes.

Hepatocytes and Kupffer cells being the main sites for dengue virus infection.³ as confirmed in biopsies and autopsies of fatal cases.¹³Cellular apoptosis is the consequence of injury due to dengue virus.¹⁴

Remnant of apoptosis are cells in form the Councilman Bodies. Repeated infections with different type of Dengue serotypes result in intensification of immune reaction. This magnification of immune reaction is accountable for causation of severe dengue infection. Antibody dependant enhancement is responsible for a serious Dengue manifestations in form of DHF and DSS.¹⁵

Presently the exact mechanism by which the immunity of the patient acts against himself is not accurately known. However we do know that T Cells have a role to play in damaging the Liver by interaction between antibodies and the endothelium, resulting in a cytokine storm .

Elevated levels of dengue virus in the body are associated with dissemination of the virus to multiple organs including Liver.¹⁶

In our study PT was deranged in 50% children in DHF group and 10% children in DF group. This is highly significant. Riaz et al reported deranged PT in 22% patients Of DHF.K Jagdishkumar et al observed abnormal PT in 30.7% cases of DHF.¹⁷

References:

1. World Health Organization. Dengue- guidelines for diagnosis, treatment, prevention and control. New Edition. Geneva: World Health Organization Publishers; 2009. p. 4-6.
2. Parkash O, Almas A, Jafri SM et al. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterol 2010; (10): 43.
3. Karoli R, Fatima J, Siddiqi Z, Kazmi KI, Sultania AR. Clinical profile of dengue infection at a teaching hospital in North India. J Infect Dev Ctries 2012;(6): 551-554.
4. Saha AK, Maitra S, Hazra SC. Spectrum of hepatic dysfunction in 2012 dengue epidemic in Kolkata, West Bengal. Indian J Gastroenterol 2013; 32: 400-403.
5. Kuo CH, Tai DI, Chang-Chien CS et al. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992; (47): 265-270.
6. Nath P, Agrawal DK, Mehrotra RM. Ultrastructural changes in skeletal muscles in dengue virus-infected mice. J Pathol 1982; 136: 301-305 .
7. Lee LK, Gan VC, Lee VJ et al. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. PLoS Negl Trop Dis 2012; 6.
8. Wahid SF, Sanusi S, Zawawi MM. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health 2000; (31): 259-263.

Conclusion:

Laboratory parameters such as serum PT,AST and ALT were measured which proved to be statistically significant in predicting Severe Dengue in form of DHF and DSS. Since many infections of Dengue start with Sore throat and conjunctivitis along with fever and myalgia,it can be mistaken for Simple Upper respiratory tract Infection or Viral fever. Hence it is important to keep high index of suspicion and get relevant tests done.

Once diagnosed as Dengue, since most of the children are anicteric ,it is recommended that At least AST,ALT and PT tests should be done(keeping in mind the Financial burden of common man) . These Liver function tests can help the clinician to anticipate the problem, prognosticate and decide the need for referral to higher centre, thus limiting mortality and morbidity. It will also help to make appropriate strategies and plans to forecast any outbreaks in future.

9. G Malvinge,PK Ranatunge et al.Patterns of Disease in SriLankan Dengue Patients. *Arc Dis Child* 2006;(91):396-400
10. Souza LJ ,Alves JG,Neto R. Aminotransferases changes and acute hepatitis in patients with fever: analysis of 1585 cases .*Braz .J.Infect.Dis.*2002,6(6):322-7.
11. Wong M,Shen E.The utility of Liver Function Test in Dengue.*Ann Acad Med Singapore* 2008,37(1):82-3.
12. M Narayanan,M Arvind,N Thilothammal .Dengue Fever Epidemic in Chennai-A Study of Clinical and Outcome. *Indian Pediatr.*2002;(39):1027-1033.
13. Huerre MR, Lan NT, Marianneau P et al.Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. *Virchows Arch* 2001; (438): 107-115
- 14.Couvelard A, Marianneau P, Bedel C et al. Report of a fatal case of dengue infection with hepatitis: demonstration of dengue antigens in hepatocytes and liver apoptosis. *Hum Pathol* 1999 ;(30): 1106-1110.
- 15.Halstead SB, O'Rourke EJ. Antibody-enhanced dengue virus infection in primate leukocytes. *Nature* 1977;(265): 739-741.
16. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. *Clin Microbiol Rev* 2009; (22): 564-581.
17. K Jagdishkumar,P Jain,G Vaddambal, Hepatic involvement in dengue fever in children, *Iranian J of Pediatrics*,2012;(22):231-236.