WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 2252-2258. Research Article ISSN 2277– 7105

LIVER DERANGEMENT IN DENGUE FEVER ADMITTED IN A TERTIARY CARE HOSPITAL IN 2014, IN KOLKATA, WEST BENGAL

Dr. Ashis Kumar Saha*[1] and Dr. Payodhi Dhar[2]

[1]M.D. (Cal), D.T.M & H (Cal), FICP, FACP. Associate Professor, General Medicine K P C Medical College, Jadavpur, Kolkata.

[2]M.B.B.S (Cal) Junior Resident, Medicine K P C Medical College, Jadavpur, Kolkata.

Article Received on
17 June 2015,

Revised on 08 July 2015,
Accepted on 29 July 2015

***Correspondence for Author**
Dr. Ashis Kumar Saha
M.D. (Cal), D.T.M & H (Cal), FICP, FACP.
Associate Professor,
General Medicine K P C Medical College,
Jadavpur, Kolkata.

ABSTRACT

Dengue fever usually affects liver; it may be in mild form or may be in very severe form, latter form usually occurs in dengue hemorrhagic fever (DHF) or dengue hemorrhagic shock (DSS). This liver involvement usually occurs during the course of transient viremia. Our aim is to evaluate the grade of liver involvement with or without serosal involvement in the form of ascites or pleural effusion. In our hospital, total 404 serologically proved patients with dengue fever admitted, of which. Among them, 136 DHF and 24 DF have ALT level >75 IU/L, whereas, 65 DHF and 3 DF patients have ALT >150 IU/L. Again, among 65 DHF patients, 40, 15 and10 patients showed ALT level >150-300 IU/L, >300-450 IU/L and >450 IU/L respectively. These patients presented with signs and symptoms resembling viral hepatitis, DHF patients showed associated ascites, pleural effusion, raised INR ≥1.5, severe albuminemia. Males showed significantly raised AST >5 times than normal, AST having >75-150 and >450 IU/L, hepatomegaly, ascites. But negative viral serology helped us to diagnose these cases as hepatitis due to dengue virus infection.

KEYWORDS: Liver involvement, Serosal involvement, Dengue fever, Dengue hemorrhagic fever, Kolkata,

INTRODUCTION

Dengue fever, an arthropod borne disease, developed from the bite of Aedes mosquito in the afternoon. This virus has four serotypes, these are DV1, DV2, DV3 and DV4. The affected patients may present subclinical infection, uncomplicated dengue fever or severe form,

dengue hemorrhagic fever and dengue shock syndrome.[1,2] In DHF, there is evidence of vascular endothelial dysfunction associated with disorders of clotting factors.[3,4] During uncomplicated DF or DHF, there is increased level of viremia, which is associated with involvement of different organs of the body, like, liver and brain. This phenomenon mostly occurs in DHF.[5] Of all the involved organs of the body, liver is the commonest. The involvement may be due to direct toxic effect of the virus itself or disordered immune response to the virus in presence of some other risk factors, like, human race, diabetes, hemoglobinopathies, and presence of hepatotoxic drugs or pre-existing liver damage.[6] Our aim in this study was to evaluate the hepatic injury by comparing hepatic enzymes, International normalized ratio (INR) with clinical presentation and platelet count.

Methods: This study was conducted only after getting permission from the local ethical committee. Total four hundred and four patients with NS_1 antigen and/or dengue immunoglobulin M antibody positive (IgM) were admitted in Kali Pada Chowdhury Medical College and Hospital between September to November 2014. After getting proper consent from the patient's party, history and thorough clinical examination was done. History of intake of hepatotoxic drugs was taken. Immediately after admission, blood was drawn for hematological, hepatitis viral serology and biochemical examination. These tests were repeated after 48 hours. 24 hours admission, imaging studies, like, chest x-ray and Ultrasonography were performed. All the demographic data, clinical, hematological, biochemical and imaging data were collected. Reference level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are 20-35 IU/L and 10-25 IU/L respectively.

Statistical analysis

Statistical method used

1. 95% confidence interval for different percentage
   $(p_1—p_2)\pm1.6SE\ (p_1—p_2)$, where $SE\ (p_1—p_2) = \sqrt{[\{p_1\ (1—p_1)/n_1\} + \{p_2\ (1—p_2)/n_2\}]}$
2. 'p' values showed maximum probability for a given level of significance.

RESULTS

In this study, we have recorded the cases, whose ALT level was more than two times normal, because, it is an indicator of hepatic involvement. The number of DF and DHF patients with ALT level >75 IU/L were 24 and 136 respectively. In patients with ALT level >75 IU/L, the common presentations in DHF and DF were fever (93.38% vs. 100%), nausea/vomiting (49.26% vs. 37.5%), anorexia (33.82% vs. 20.83%) and pain abdomen (21.5% vs. 37.5%)

respectively. Proportion of liver involvement was nearly equal in DHF and DF (40.44% vs. 37%). Again, ascites and pleural involvement was only present in DHF. [Table I]. Three patients of DF showed ALT level >150 IU/L (ALT level more than five times normal). But the number of DHF patients with ALT level >150 IU/L was 65 in all age groups having an evidence of serosal involvement in the form of ascites, pleural effusion, which was present in 38.46% and 32.30% of these patients respectively. The biochemical parameters in the form of INR ≥1.5, albumin <3.5 gram/dl as 20% and 7.69% respectively and platelet count >15.38% were recorded [Table II]. In males,, AST levels was significantly raised than females (64 out of 232 vs. 23 out of 172, p<0.00). Males showed significantly elevated ALT level >75 IU/L to 150 IU/L (70 out of 232 vs. 25 out of 172, p<0.00) and >450 IU/L (10 out 232 vs. 0 out of 172, p<0.00) than females. Significant number of males showed hepatomegaly (73 of 232 vs. 37 of 172 patients) and ascites (24 of 232 and 8 of 172 patients). But no significant sex difference was seen in the level between >150 IU/L and 450 IU/L. Since no death was recorded from in this study, all the patients were gradually recovered from the hepatic involvement within one to two weeks both in the form liver size and enzyme status.[Table III].

Table I: Comparison of symptoms and signs in DHF and DF having ALT level >75 IU/L

Item	DHF(136) 33.65%	%	DF(24)	%	Confidence interval	P value	Significance
Pain abdomen	29	21.32	9	37.5	-0.346-0.022	0.086	NS
Nausea/vomiting	67	49.26	9	37.5	-0.099-0.334	0.287	NS
Anorexia	46	33.82	5	20.83	-0.072-0.332	0.208	NS
Fever	127	93.38	24	100	-0.166-0.033	0.194	NS
Bleeding	3	2.20	0	0	-0.036-0.080	0.462	NS
Hepatomegaly	55	40.44	9	37.5	-0.183-0.242	0.786	NS
Ascites	32	23.52	0	0	0.061-0.408	0.007	Significant
Pleural effusion	40	29.41	0	0	0.106-0.482	0.002	Significant
Albumin	11	8.08	0	0	0	0.00	Significant

NS: Non-significant

Table II: Comparisons of signs and biochemical parameters in DHF patients with ALT>150 IU/L

Items	Age (1-18 years)	Age (>18-40 years)	Age (>40–60 years)	Age >60 years	Total patients (65)	Percentage
Signs						
Heapatomegaly	0	27	9	3	39	60
Pleural effusion	0	13	6	2	21	32.30

Ascites	0	17	2	2	25	38.46
Biochemical examinations						
Bilirubin >5 mg%	0	0	0	0	0	0
INR ≥1.5	0	3	0	13	13	20
Albumin <3.5 gm%	0	5	0	5	5	7.69
Platelets <40000/cc	0	2	2	10	10	15.38

Table III: Comparative study of hepatic and serosal involvement between males and females with dengue fever

Liver involvement	Males(232)	Females(172)	Total patients(404)	Percentage	P value	Significance
AST (IU/L) >5 times normal	64	23	87	21.53	0.00	Significant
ALT (IU/L)						
>75-150	70	25	95	23.51	0.00	Significant
>150-300	28	12	40	9.9	0.09	NS
>300-450	9	6	15	3.71	0.83	NS
>450	10	0	10	2.47	0.00	Significant
Hepatomegaly	73	37	110	27.22	0.02	Significant
Serosal involvement						
Ascites	24	8	32	7.92	0.02	Significant
Pleural effusion	27	13	40	9.90	0.17	NS

NS: Non-significant

DISCUSSION

Liver is usually involved in dengue fever, specially complicated dengue fever, both in DHF and DSS. In liver involvement, there is evidence of hepatomegaly, elevations of liver enzymes (AST, ALT and Alkaline phosphatase), INR and Prothrombin time with or without elevation of bilirubin. In our study, symptoms like abdominal pain, fever, anorexia, nausea/vomiting with elevation of liver enzymes, raised Prothrombin time and INR were demoed. So, there may be confusion with infective hepatitis. But, associated thrombocytopenia and positive dengue serology (NS_1 antigen and/or IgM dengue antibody positive) and negative serology for hepatitis A, B, C, E viruses ruled out the infectivity with hepatitis viruses. But various studies in the world, showed the elevation of AST and ALT between 36.4% and 96% in all age groups especially in DHF and DSS.[7-12] But large population studies in Brazil demonstrated increased level of AST and ALT in 63% and 45% patients respectively with tenfold rise in ALT in 3.8% of patients. Other studies showed wide

variation of percentage of patients between 1.8% and 11.2% having more than tenfold rise in ALT levels[11, 12], whereas, our study showed 10.4% patients showed more than 10 fold rise in ALT, which was similar to that demoed in 2012 epidemic study in Kolkata by Saha et al.[13] In our study, 24 DHF patients showed ALT level more than 75 IU/L, but, 3 DF patients showed ALT level more than 150 IU/L. Similarly, AST level more than 5 times than normal was found in 21.53% of patients, amongst them, 3 DF patients had such high level of AST. But in the study done by Saha et al., no DF or DHF patients showed AST and ALT levels above 150 IU/L.[13] This AST rise may be due to myocyte involvement[14, 15]. In our study, INR of >1.5 was demoed in 20% of DHF patients, which was similar to the study done by Saha et al and Kumar et al.[13, 16]

In our study, Significant number of male patients showed AST level >5 times normal, ALT level >75-150 IU/L and >450 IU/L, hepatomegaly and ascites. On the contrary, previous study done by Saha et al. demonstrated only significant difference in case of ALT level >75-150 IU/L.

In our study, evidence of hypoalbuminemia was demonstrated in 7.69% of cases, which was significantly low as compared to the study done by Saha et al. (12.94%) and Wong and Shen (16.5%).[13,17] On the contrary, very high percentage of hypoalbuminemia was evidenced in the study done by Itha et al.[8]

Surprisingly, in our study, bilirubin level was normal in DF and DHF patients which was contrary to the study done by Saha et al. in 2012 epidemic in Kolkata and Nimmannitya.[13,18] Among all the mechanisms of liver injury, direct toxic effect of virus and altered immune mechanism to virus-infected hepatocytes are the most important causes. Other causes are circulatory failure, hypotension and localized vascular leakage producing anoxia or metabolic acidosis.[7, 8, 14, 18] This virus is hepatotropic as evidenced by the presence of nucleic acid and antigen of dengue virus in the hepatocytes.[19]

Our study showed only three of 136 DHF patients (2.20%) showed evidence of heamatemesis and melena, which may be due to hepatic derangement in the form of raised INR (>1.5) and ALT level or thrombocytopenia. According to Wong et al. liver damage may be due to DHF, DSS, and thrombocytopenia, secondary infection in female sex or child.[17]

In our study, with ALT level of >75 IU/L, the percentage of ascites and pleural effusion were 23.52% (32 in 136 DHF patients) and 29.41% (40 out of 24 DF patients) respectively. But, when we collected the patients with ALT level >150 IU/L, the percentage were increased up to 32.30% (21 out of 65 DHF patients) and 38.46 (25 out of 65 DHF patients) respectively. So, here the ascites and pleural effusion may be due to decreased production of albumin by damaged hepatocytes.

Our major drawback of this study was absence of liver biopsy. So, to detect the nature of pleural effusion, serum-pleural fluid albumin gradient (SPAG) estimation should be done.

CONCLUSION

Hepatic involvement in the dengue fever may be subclinical, mild, moderate or severe. There was hepatomegaly with mild rise in ALT. But, in case of more than 10 fold rise in ALT in DHF patients, there was evidence of significant development of ascites and pleural effusion. It may be due to severe hypoalbuminemia and associated capillary leakage. Again, thrombocytopenia due to dengue virus infection and moderate t6o severe hepatic dysfunction may be responsible for bleeding disorders. So, in dengue endemic area, hepatic involvement associated with raised enzymes in absence of negative hepatitis viral profile may be suspected as dengue virus induced hepatitis, which can be confirmed by positive serology for dengue fever.

REFERENCES

1. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill. 2010; 15: 19509.
2. Whitehorn J, Farrar J. Dengue. Br Med Bull, 2010; 95: 161-173.
3. Sundravally R, Narayanan P, Bhat BV, et al. Fulminant faiure in an infant with severe dengue infection. Indian J Pediatr, 2010; 77: 435-437.
4. Varathraj A. Encephalitis in the clinical spectrum on dengue infection. Neurol India. 2010; 58: 585-591.
5. Martina BE, Koraka p, Octerhaus AD. Dengue virus pathogenesis: an integrated view. Clin Microbiol Rev. 2009; 22: 564-581.
6. George RLLCS. Clinical spectrum of dengue infection. Washington: Gab International; 1997.
7. Mohan B, Patwari AK, Anand VK. Hepatic dysfunction in childhood dengue infection. J Trop Pediatr, 2000; 46: 40-43.

8. Itha S, Kashyap R, Krishnani N et al. Profile of liver involvement in dengue virus infection. Natl Med J India, 2005; 18: 127-130.
9. Faridi MM, Aggarwal A, Kumar M, Sarafra A. Clinical and biochemical profile of dengue haemorrhagic fever in chidren in Delhi. Trop Doct. 2008; 38: 28-30.
10. Wahid SF, Sansui S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southest Asian J Trop Med Pub Health. 2003; 31: 259-263.
11. Kuo CH, Tai DI, Chang-Chein CS, et al. Liver biochemical test and dengue fever. Am J Trop Med Hyg, 1992; 47: 265-270.
12. Souza LJ, Alves JG, Nogueira RM, et al. Aminotransferase changes and Acute hepatitis in patients with dengue fever: analysis of 1,585 cases. Braz J Infect Dis. 2004; 8:156-163.
13. Ashis Kumar Saha, Soumitra Maitra, Subhas Hazra. Spectrum of hepatic dysfunction in 2012 dengue epidemic in Kolkata, West Bengal, 2013; 32(6): 400-403.
14. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infection. Trans R Soc Trop Med Hyg. 2006; 100: 608-614.
15. Trung DT, Yhu Thao LT, Hien TT, et al. Liver involvement associated with infection in adultin Vietnum. Am J Trop Med Hyg. 2010; 83: 774-780.
16. Jagadishkumar, K, Jain P, Manjunath Vg, Umesh L. Hepatic involvement in dengue fever in children. Iran J Pediatr, 2012; 22:231-236.
17. Wong M, Shen E. The utility of liver function tests in dengue. Ann Acad Med, 2008; 37: 82-83.
18. Nimmannitya S, Thisy U, Hemscichart V. Dengue haemorrhagic fever with unusual manifestations. Southest Asian J Trop Med Public Health, 1987; 18: 398-405.
19. Vazquez-Pichardo M, Rosales-Jimenez C, Rojas-Espinosa O et al. Is liver damage dependent on the serotype of dengue virus? A study in Mexico. Dengue Bulletin, 2006; 30: 114-119.