Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Original Research Article

A Study to Assess the Prevalence of Hepatobiliary Dysfunction and Ultrasonographic Abnormalities Related to Dengue Fever in Pediatric Age Group.

Dr. Vinod Kumar Mishra[1], Dr. Mithilesh Pratap[2], Dr. Sanjeev Kumar[3], Dr Tushar Kumar[4]

[1]Associate professor, Department of Paediatrics, Vims, Pawapuri, Nalanda, Bihar, India.

[2]Associate professor and HOD, Department of Radiology, Vims, Pawapuri, Nalanda, Bihar, India.

[3]Assistant professor and HOD, Department of Paediatrics, Vims, Pawapuri, Nalanda, Bihar, India.

[4]Senior Resident, Department of Radiology, Vims, Pawapuri, Nalanda, Bihar, India.

Corresponding Author: Dr Tushar Kumar

Received: 21-08-2021 / Revised: 05-09-2021 / Accepted: 27-09-2021

Abstract

Aim: The aim of the present study to evaluate the prevalence of hepatobiliary dysfunction and ultrasonographic abnormalities in dengue fever in pediatric age group.

Methods: The Prospective, Observational study was conducted in the Department of pediatrics, Vardhman institute of medical sciences, Pawapuri, Nalanda, Bihar, India, for 18 months. 120 Children below 18 years who were Dengue Non structural antigen protein 1 [NS1] and/or Immuno- globulin M [IgM] positive only were included in the study. After clinical assessment, the patients were classified as DF/DHF/DSS. Lab investigations included CBC, WBC count, platelet count, hematocrit, SGOT, SGPT, PT, APTT and INR was monitored.

Results: In the present study, mean SGOT and SGPT in DSS was statistically significant. Total serum bilirubin was increased in DSS than in DHF. Total protein, albumin, globulin and ALP were statistically insignificant. Coagulation profile was increased in all the 3 groups. The mean SGOT/SGPT in DHF was 107.11±48.36 and 66.78±35.98 and in DSS was 241.25±121.22and 195.12±102.25 with was statistically significant.Total protein, albumin, globulin, and alkaline phosphatase levels in all the 3 groups were not statistically significant, however bilirubin levels were higher in DSS when compared to DHF. Ascites, hepatomegaly, pleural effusion and gall bladder thickening findings in ultrasound were statistically significant in DSS when compared to DHF. USG showed ascites, pleural effusion, hepatomegaly, gall bladder thickening which were statistically significant in DSS than in DHF.

Conclusion: The clinical and laboratory markers are helpful for diagnosing and predicting the course of the disease.

Keywords: hepatobiliary dysfunction, dengue fever, USG

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Introduction

Dengue virus infection is a major and important public health problem in many South East Asian countries and also in more than 100 countries of tropical and subtropical region.[1,2]
Two–fifths of the world's population or 2500 million people are now at risk for dengue, and every year approximately 50 million new cases occur worldwide.[3]

The global prevalence of dengue infection has increased dramatically in the recent decades.[4] Recently an increasing trend of outbreaks of DF and its complicated forms has been reported in India.[3] Occurrence of Dengue fever (DF) in the country was first reported during 1956 from the district of Vellore in Tamil Nadu. Dengue is prevalent throughout India in urban as well as rural areas. According to latest data there are 64058 cases and 135 deaths from dengue in 2015.[5] Typically, people infected with dengue virus are asymptomatic (80%). They may have mild symptoms such as an uncomplicated fever.[6] Hepatic injury with dengue infection has been described since 1967.[7] Liver dysfunction in patients with dengue varies from mild injury with elevation of transaminase activity. Hepatomegaly (tender/non tender) to severe hepatocyte injury resulting in jaundice may also occur.[1] Hepatic dysfunction is caused by a direct effect on liver cells or as a consequence of deranged host immune response against the virus. Other factors including race, diabetes, haemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs may also play a role.[8] The mechanism may be prolonged shock, metabolic acidosis and DIC in complicated dengue causing ischemia resulting in severe hepatic dysfunction.[9] There are isolated case reports of fulminant hepatic failure in dengue patients. But the derangements in the transaminases are usually self-limiting.[10] Dengue infection causes liver parenchyma damage.[11] Rising of aminotransferase level occurs in the acute phase of the disease. Liver enzyme levels subsequently decrease as the liver recovers.[12] Elevated liver enzymes in dengue is an early marker of dengue infection. It is also a predictor for assessing the disease severity.[13]

Material and methods

The Prospective, Observational study was conducted in the Dept of pediatrics, Vardhman institute of medical sciences, Pawapuri, Nalanda, Bihar, India, for 18 months, after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

120 Children below 18 years admitted to pediatric ward at our hospital with acute onset high grade fever were included by simple random sampling.
A questionnaire was used, where all the symptoms and lab investigations were entered and checked by the investigators.

Children who were Dengue Non structural antigen protein 1 [NS1] and/or Immuno- globulin M [IgM] positive only were included in the study. Children with other diseases like enteric fever, rickettsial fever, malaria, leptospirosis, septicemia and other viral hemorrhagic fevers were excluded from the study. Liver enzymes (SGOT & SGPT), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), total protein, albumin, globulin, serum bilirubin, alkaline phosphatase, USG abdomen findings ascites, pleural effusion, hepatosplenomegaly and gall bladder thickening. Fever, nausea, pain abdomen, hepatomegaly, splenomegaly, bleeding, pleural effusion, shock, jaundice, encephalopathy. After clinical assessment, the patients were classified as DF/DHF/DSS. Lab investigations included CBC, WBC count, platelet count, hematocrit, SGOT, SGPT, PT, APTT

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

and INR was monitored. Monitoring of hepatic and ultrasonographic parameters were done. Cut off value of prolonged activated partial thromboplastin time (APTT) was 38 second, elevated serum aminotransferase levels (aspartate amino trans-ferase (AST) or alanine aminotransferase (ALT) were >39 U/L). Liver enzymes and ultrasonographic parameters in DF/DHF/DSS were compared in the study.

Statistical methods: The results were analyzed using standard normal test and student 't'test.

Results

In the present study, mean SGOT and SGPT in DSS was statistically significant. Total serum bilirubin was increased in DSS than in DHF. Total protein, albumin, globulin and ALP were statistically insignificant. Coagulation profile was increased in all the 3 groups.

Table 1: SGOT, SGPT levels in Dengue fever.

	DF(N=40)	**DHF**(N=64**)**	**DSS**(N=16)	P-value
	Mean±SD	Mean±SD	Mean±SD	
SGOT(U/L)	95.55±68.22	107.11±48.36	241.25±121.22	0.0001*
SGPT(U/L)	54.54±24.78	66.78±35.98	195.12±102.25	0.0001*

The mean SGOT/SGPT in DHF was 107.11±48.36 and 66.78±35.98 and in DSS was 241.25±121.22and 195.12±102.25 with was statistically significant.

Table 2: Prothrombin time/INR, Activated partial thromboplastin time in dengue

	DF(N=40)	**DHF**(N=64**)**	**DSS**(N=16)	P-value (DHF vs DSS)
	Mean±SD	Mean±SD	Mean±SD	
APTT (seconds)	26.7±4.1	34.5±5.7	39.9±6.2	0.005*
PT/INR	1.1±0.3	1.2±0.3	1.4±0.3	0.002*

The values of PT/INR/APTT was progressively more in 3 groups.

Table 3: Protein, bilirubin and alkaline phosphatase abnormalities in dengue

	DF(N=40)	**DHF**(N=64**)**	**DSS**(N=16)	P-value (DHF vs DSS)
	Mean±SD	Mean±SD	Mean±SD	
Total protein (gm/dl)	7.11±0.91	6.31±0.66	6.31±0.59	0.77
Albumin (gm/dl)	5.02±0.54	4.50±0.55	4.44±0.55	0.44
Globulin (gm/dl)	2.44±0.55	2.44±0.33	2.11±0.87	0.96
Bilirubin (mg/dl)	1.1±0.6	1.1±0.8	2.1±1.4	0.007*
Alkaline phosphatase (IU/L)	189.12± 188.3	371.45±189.55	466.98±229.69	0.14

Total protein, albumin, globulin, and alkaline phosphatase levels in all the 3 groups were not statistically significant, however bilirubin levels were higher in DSS when compared to DHF.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table 4: Ultrasonographic abnormalities in dengue fever

	DF(N=40) N (%)	**DHF**(N=64) N (%)	**DSS**(N=16) N (%)	P-value (DHF vs DSS)
Ascites	0(0)	22(34.37)	13(81.25)	0.0069*
Hepatomegaly	8(20)	28(43.75)	13(81.25)	0.044*
Splenomegaly	0(0)	16(25)	5(31.25)	1.2
Pleural effusion	0(0)	8(12.5)	11(68.75)	0.00008*
GB thickening	0(0)	4(6.25)	13(81.25)	0.000001*

*P<0.05 is statistically significant

Ascites, hepatomegaly, pleural effusion and gall bladder thickening findings in ultrasound were statistically significant in DSS when compared to DHF. USG showed ascites, pleural effusion, hepatomegaly, gall bladder thickening which were statistically significant in DSS than in DHF. (Table 1-4).

Discussion

Dengue is a major public health concern throughout the tropical and subtropical regions of the world. According to WHO, 50-100 million cases were estimated to occur annually in more than 100 endemic countries. Recurring outbreaks of DF/DHF in India have been reported from various states including Andhra Pradesh, Karnataka, Kerala and Maharashtra. Various mechanisms are proposed to explain signs and symptoms such as complex immune mechanism, T-cell mediated antibodies cross reactivity with vascular endothelium, enhancing antibodies, complement and its products and various soluble mediators including cytokines and chemokines. Whatever the mechanisms are, these ultimately target vascular endothelium, platelets and various organs leading to vasculopathy and coagulopathy responsible for the development of haemorrhage and shock.[14] Hepatic dysfunction in the form of marked elevated liver enzymes were higher in severe and complicated dengue in comparison to classical dengue fever. The degree of liver dysfunction in children with dengue infection varies from mild injury with elevation of transaminases to severe injury with jaundice and liver cell failure. In dengue, the rise of AST is usually more than ALT. By follow-up, AST levels return to normal levels in most of the cases. On the other hand ALT levels remain slightly increased above the normal cut-off value in approximately one- third of the patients. This pattern, with AST rising more quickly and peaking at a higher level and then returning to normal faster than ALT levels, is different from the pattern usually seen in acute hepatitis caused by hepatitis viruses. In the study done by Dhrubajyoti et al, the AST was more than ALT in DHF and DSS which was significant. Transaminases levels, particularly AST levels, have been suggested as a potential marker for differentiating dengue from other viral infections during the early febrile phase.[15] In the present study, mean AST/ALT in DHF was 107.11±48.36 and 66.78±35.98 and in DSS was 241.25±121.22and 195.12±102.25 with was statistically significant.

In a study done by Bokade et al, bilirubin, serum albumin, liver enzymes like ALT, AST, ALP were significantly raised in subjects with severe dengue as compared to other two groups. AST was raised in all the three groups and the p value was insignificant and cannot predict the severity and outcome of dengue.[16] This is in contrast to present study where it was observed that the rise of AST was significant. In study done by Tamil Selvan et al, the mean AST/ ALT was 252/124 in and 343/313 in dengue with warning signs and severe dengue respectively.[17] The findings were comparable to the present study. In a study done in Delhi in 2000, Brij

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Mohan et al says that the mean levels of the liver enzymes reached a peak and remained significantly higher during the 2nd week, and declined towards normal in the 3rd week.
Serum ALP levels also showed a similar trend. These enzymes were raised even in the absence of hepatomegaly. All the children with DSS and DHF had elevated enzymes and the mean values were significantly higher than those with DF.[18] The present study revealed that alkaline phosphatase was raised in the DHF and DSS groups. However due to lack of follow up, the trend in the alkaline phosphatase and liver enzymes was not established. In the present study, it was observed that APTT was 34.5±5.7/39.9±6.2in DHF/DSS respectively which was statistically significant. Kalenahalli et al.[19] however had found the mean APTT of 34 and 33 in DHF/DSS but the values were not significant. In the present study PT/ INR was significantly raised in DSS compared to DHF comparable to the study done by Kalenahalli. In the study by Dhrubajyoti, the APTT in all the 3 groups were not statistically significant. But PT/ INR was raised in DSS group, which was comparable to the present study. Therefore PT/ INR can be used as a potential marker for monitoring severity, in addition to APTT.[15] The present study reveals that the values of total protein, albumin, globulin were similar in DHF and DSS groups, whereas bilirubin was the only significant parameter to be raised. In a study done by Bokade et al, hyperbilirubinemia was found in 5.7% of cases of dengue with warning signs, and 24% of cases in severe dengue, which was significant.[16] Kalenahalli also reported that bilirubin was raised in DHF and DSS cases, whereas globulin was more in DHF and DSS cases compared with DF.[19]

Ultrasonography is a safe, low-cost imaging method that does not utilize ionizing radiation, with high sensitivity to detect early signs of plasma leakage. Particularly pleural effusion, may be early identified, up to two days before defervescence, preceding changes in hematocrit levels. Sonographic findings express the increase in capillary permeability (a sign of plasma leakage) and include cavitary effusion (ascites, pleural and pericardial effusion), and gallbladder wall thickening present in one third of patients affected by the mild presentation, and in 95% of cases with the severe presentation of DHF. Additionally, the presence of fluid in the perirenal space can be visualized. Splenomegaly, hepatomegaly and volumetric increase of the pancreas may also be observed.[20] In a study done in a medical college in Bengaluru, Santosh et al suggests that sonographic features of thickened GB wall, pleural effusion (bilateral or right side), ascites, hepatomegaly and splenomegaly should strongly favor the diagnosis of dengue fever in patients presenting with fever and associated symptoms, particularly in an epidemic.[21]

Ascites, splenomegaly, pleural effusion and gall bladder thickening findings in ultrasound were found in DHF and DSS. However hepatomegaly was found in all the 3 groups. Bokade et al has also shown that hepatomegaly is present in all the 3 groups of dengue fever.[16] Baskar et al and Surangrat et al have reported that pleural effusion and ascites are present more in DHF and DSS groups.[22,23] In a study done by Dhrubajyoti, the author mentions that gall bladder wall thickening is present in all the 3 varieties of dengue fever, about 50% of cases in DF and 80% of cases of DHF and DSS.[15] The epidemiological characteristics of patients or differences in dengue viruses.

Conclusion

The present study concluded that the clinical and laboratory markers are helpful for diagnosing and predicting the course of the disease. Involvement of liver can range from asymptomatic elevation of liver enzymes to liver dysfunction according to the stage of dengue infection.

Severity of dengue infection can be assessed reasonably by ultrasonographic parameters like ascites, pleural effusion and gall bladder thickening, which can precede the laboratory markers.

Reference

1. Wiwanitkit V. Liver dysfunction in dengue Infection, an analysis of previously published Thai cases. *J Ayub Med Coll Abbottabad*. 2007;19(1):10-12.
2. Kumar R, Tripathi P, Tripathi S, Kanodia A, Venkatesh V. Prevalence of dengue infection in North Indian Children with acute hepatic failure. *Annals of Hepatology*. 2008;7(1):59-62.
3. Petedachai W. Hepatic dysfunction in children with dengue shock syndrome. *Dengue Bulletin*. 2005;29:112-18.
4. Yewale VN, Gopinath S. Dengue Fever. *IAP speciality series on Pediatric Infectious Diseases*. 2006.271-286.
5. www.nvdcp.gov.in/dengue
6. Whitehorn J, Farrar J. Dengue. *Br Med Bull*. 2010;95(1):161-73.
7. Martina BEE, Koraka P, OsteMunasinghe DR, Rajasuriya K. Hepatitis in dengue fever. *Ceylon Med J*. 1967;12(4):222-23.
8. Ageep AK. Degree of liver injury in Dengue virus infection. *Journal of General and Molecular Virology*. 2012;4(1):1-5.
9. Halstead SB. Dengue Fever and Dengue Haemorrhagic Fever: Behrman R.E., Kliegman R.M, Jenson HB, Bonita F. Stanton. Nelson Textbook of Pediatrics, 18th Edition, Philadelphia: Saunders, 2008.1412-1414
10. Sedhain A, Adhikari S, Regmi S, Chaudhari SK, Shah M, Shrestha B. Fulminant hepatic failure due to dengue. *KUMJ*. 2011;9(34):73-75.
11. Itha S, Kashyap R, Krishnani N, Saraswat V, Choudhari G, Aggarwal R. Profile of liver involvement in dengue virus infection. *The National Medical Journal of India*. 2005;18 (3
12. Trung DT, Thao LT, Hien TT, Hung NT, Vinh NN, Hien PT, et al. Liver involvement associated with dengue infection in adults in Vietnam. *American J Trop Med Hyg*. 2010;83(4):774-80.
13. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. *Trans R Soc Trop Med Hyg*. 2006;100:608-14.
14. National Guidelines for Clinical Management of Dengue Fever. WHO, 2014. www.nvbdcp.gov.in (accessed on 10th July 2018).
15. Bandyopadhyay D, Chattaraj S, Hajra A, Mukho- padhyay S, Ganesan V. A Study on Spectrum of Hepatobiliary Dysfunctions and Pattern of Liver Involvement in Dengue Infection. J Clin Diagn Res. 2016 May; 10(5):OC21-6. doi: 10.7860/JCDR/2016/ 16946. 7784. Epub 2016 May 1
16. Bokade C M., Chauhan Urmila and Kamat Pranoti. 2016, Study of Hepatic Dysfunction In Dengue Fever And It's Predictor of Outcome. Int J Recent Sci Res. 7(9), pp. 13360-13363.
17. Selvan, Tamil &Lp, Joy & Souza, D & Swamy, Narayana & Kumar, Mahesh. (2015). ISSN 2347-954X(Print) Prevalence and severity of Thrombocytopenia in Dengue fever in children.
18. Mohan B, Patwari A. K, and Anand V.K. Hepatic Dysfunction in Childhood Dengue Infection, Journal of Tropical Pediatrics,Volume 46, 2000 Feb;40-45.
19. Jagadishkumar K, Jain P, Manjunath VG, Umesh L. Hepatic involvement in dengue Fever in children.Iran J Pediatr. 2012 Jun; 22(2):231-6.
20. Villar Barbosa de Oliveira, Ricardo & Rios, Lívia & dos Remédios Freitas Carvalho Branco, M & Braga Jr, L.L. & Moucherek Soares Nascimento, Janílson & Fontinelle Silva, Gilnara & Pinto Bandeira, Kemuel. (2010). Usefulness of ultrasonography in children with

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

suspected dengue hemorrhagic fever: A literature review. Radiologia Brasileira. 43. 401-407.
21. Santhosh VR et al,J Clin Imaging Sci. 2014 Mar 21;4:14. doi: 10.4103/2156-7514.129260. eCollection 2014.
22. Baskar C, Babu A.S.K.K.., Heber Anandan Clinical profile and outcome of dengue fever in pediatrics Paripex-Indian Journal Of Research, Volume : 5 | Issue : 10 |October 2016.
23. Surangrat Pongpana, Apichart Wisitwong, Chamaiporn Tawichasri, Jayanton Patumanond Prog- nostic Indicators for dengue infection severity, Int J Clin Pediatr• 2013;2(1):12-18.