Original Research Article

Prevalence of hepatobiliary dysfunction and ultrasonographic abnormalities in dengue fever in pediatric age group

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Abstract

Introduction: High morbidity and mortality in DF/DHF is due to multiorgan involvement. Hepatic involvement can present with varied manifestations ranging from hepatomegaly to fulminant hepatic failure. Incidence of hepatic dysfunction is more in Dengue shock syndrome and Dengue hemorrhagic fever. Ultrasound can be used as a prognostic indicator and also used as means of monitoring for plasma leakage. **Objectives:** To study the clinical presentation, hepatic abnormalities and the ultrasonographic findings in dengue fever, dengue haemorrhagic fever and dengue shock syndrome and to correlate these findings with the severity of dengue fever. **Materials and Method**s: 100 hospitalized patients of Dengue fever were classified as DF/DHF/DSS as per their clinical manifestations. Lab investigations namely SGOT, SGPT, PT, APTT and INR were monitored. Ultrasonography of the abdomen and thorax were done. Hepatic enzymes, coagulation workup and ultrasonographic parameters in DF/DHF/DSS were compared in the study. **Conclusion**: Severe dengue can pose challenges to the treating physician. Hence early identification of deterioration in the clinical status can be reasonably assessed by using hepatic and ultrasound parameters which will help in the management of dengue illness and thus reducing the mortality and morbidity.

Keywords: Dengue fever, DHF, DSS, Hepatic enzymes, Ultrasonographic findings

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Introduction

Dengue fever ranks as the most important mosquito-borne viral disease in the world. The emergence and spread of all four dengue viruses (serotypes) represent a global pandemic. While dengue is a global concern, currently closeto75% of the global population exposed to dengue are in the Asia-Pacific region. It is also reported in various literatures that high morbidity and mortality in DF/DHF is due to multiorgan involvement.

Most commonly involved organs are liver, kidney, heart, lungs and brain. Based on WHO 2014 guidelines clinically dengue fever is classified into DF/DHF/DSS [1]. Hepatic involvement in dengue is known with protean manifestations ranging from hepatomegaly, elevated liver enzymes to fulminant hepatic failure [2]. The incidence of hepatic dysfunction is more in Dengue shock syndrome and Dengue hemorrhagic fever.

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Aminotransferase levels are useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding [3]. Ultrasonography (USG) of the chest and abdomen is a cheap, rapid and widely available non-invasive imaging method which can be an important adjunct to clinical profile and early diagnosis of DF prior to obtaining serologic confirmation test results [4].

The ultrasound findings in early milder form of DF include GB (gall bladder) wall thickening, pericho-lecystic fluid and hepatosplenomegaly. Severe forms of the disease are characterized by fluid collection in the perirenal and pararenal region, hepatic and splenic subcapsular fluid, more commonly generalized ascites. Ultrasound has two potential uses in the management of dengue fever. Firstly, as a prognostic indicator, used to assess which patients are at severe risk of entering the critical phase. Secondly, ultrasound is used as means of monitoring for plasma leakage (ascites, pleural effusion and perinephric edema). It is also used to know the

presence and degree of plasma leakage at various sites in the body in patients with dengue fever to facilitate early management and hence prevent fatal complications [5]. In the present study, an attempt was made to correlate the hepatic abnormalities and the ultrasonographic findings in various forms of dengue fever which can help in early diagnosis and rational treatment.

Objectives

1. To study the clinical presentation, hepatic abnormalities and the ultrasonographic findings in dengue fever, dengue haemorrhagic fever and dengue shock syndrome.
2. To correlate these findings with the severity of dengue fever.

Materials and Methods

Setting and Study design: A hospital based prospective study done over one year from November 2015- October 2016.

Study size: 100 patients.

Sampling methods: Children below 18 years admitted to pediatric ward at our hospital with acute onset high grade fever were included by simple random sampling.

Data source: For data entry, questionnaire was used, where all the symptoms and lab investigations were entered and checked by the investigators.

Inclusion criteria: Children who were Dengue Non structural antigen protein 1 [NS1] and/or Immuno-globulin M [IgM] positive only were included in the study.

Exclusion criteria: Children with other diseases like enteric fever, rickettsial fever, malaria, leptospirosis, septicemia and other viral hemorrhagic fevers.

Participants: Children admitted in pediatric department in Dr. B.R. Ambedkar Medical College in the year November 2015-October 2016.

Ethical consideration and permission: Ethical committee clearance was taken prior to study. Consent from parents/caretakers of the patients was obtained during the study.

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

Variables: Quantitative variables: 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.

Qualitative variables: Fever, nausea, pain abdomen, hepatomegaly, splenomegaly, bleeding, pleural effusion, shock, jaundice, encephalopathy.

Bias: none

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.

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 aminotrans-ferase (AST) or alanine aminotransferase (ALT) were >39 U/L). Liver enzymes and ultrasonographic parameters in DF/DHF/DSS were compared in the study.

Result

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.

	Mean±SD	Mean±SD	Mean±SD	
SGOT(U/L)	94.1±70.1	106.2±51	238.1±118.3	0.0001*
SGPT(U/L)	53.3±26.2	65.3±37.4	193.8±100.1	0.0001*

The mean SGOT/SGPT in DHF was 106.2 and 65.3 and in DSS was 238.1 and 193.8 with was statistically significant

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

	DF(N=36)	**DHF**(N=52)	**DSS**(N=12)	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=36)	**DHF**(N=52)	**DSS**(N=12)	P-value (DHF vs DSS)
	Mean±SD	Mean±SD	Mean±SD	
Total protein (gm/dl)	6.9±0.8	6.5±0.7	6.5±0.6	0.865
Albumin (gm/dl)	4.8±0.6	4.3±0.6	4.4±0.6	0.391
Globulin (gm/dl)	2.3±0.5	2.3±0.4	2.0±0.6	0.105
Bilirubin (mg/dl)	1.0±0.4	1.0±0.9	1.9±1.5	0.008*
Alkaline phosphatase (IU/L)	191.1± 178.3	367.5±192.6	464.8±232.7	0.135

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.

Table-4: Ultrasonographic abnormalities in dengue fever.

	DF(N=36)	**DHF**(N=52)	**DSS**(N=12)	P-value (DHF vs DSS)
	N (%)	N (%)	N (%)	
Ascites	0(0)	17(32.7)	9(75)	0.0071*
Hepatomegaly	7(19.4)	22(42.3)	9(75)	0.0411*
Splenomegaly	0(0)	13(25)	3(25)	1
Pleural effusion	0(0)	7(13.5)	8(66.7)	0.00009*
GB thickening	0(0)	3(5.8)	9(75)	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 1,2,3,4).

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 [1]. 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 [6]. In the present study, mean AST/ALT in DHF was 106.2 and 65.3 and in DSS was 238.1 and 193.8 which 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 [2]. 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 [3]. The findings were comparable to the present study. In a study done in Delhi in 2000, Brij 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 [7]. 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 34.5/39.9 in DHF/DSS respectively which was statistically significant. Kalenahalli et al [8], 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 [6]. 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 [2]. Kalenahalli also reported that bilirubin was raised in DHF and DSS cases, whereas globulin was more in DHF and DSS cases compared with DF[8].

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 [9]. 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 [10].

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 [2]. Baskar et al and Surangrat et al have reported that pleural effusion and ascites are present more in DHF and DSS groups [11,12]. 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 [6]. The epidemiological characteristics of patients or differences in dengue viruses.

Conclusion

Dengue infection still contributes to significant mortality and morbidity in our country. Its clinical manifestations and varied presentation poses difficulty in diagnosing the condition. 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.

What does this study adds to existing knowledge?

There are many separate studies in adult population regarding hepatobiliary dysfunction and ultrasound in dengue, but data in paediatric population, especially from South India are few. The present study combines the parameters of hepatobiliary dysfunction and USG in diagnosing dengue. Ultrasound can diagnose fluid leak phase earlier than serological markers which correlates well with the severity of dengue.

Contribution of authors- MSR, PR, SMG were responsible for conceptualization, management of cases and writing the article. GM contributed in review of literature.PM did the statistical analysis.

List of abbreviations- DF- dengue fever, DHF- dengue hemorrhagic fever, DSS- dengue shock syndrome, SGOT- serum glutamic oxaloacetic transaminase, SGPT- serum glutamic pyruvic transaminase, PT- prothrombin time, APTT- activated partial thromboplastin time, INR- international normalized ratio, ALP- alkaline phosphatase

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