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Original Article

Role of ultrasound in early prediction of severity of dengue infection

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ABSTRACT

Background: Dengue has become a major international health problem in recent years. As per the World Health Organization, dengue has shown a 30-fold increase globally over the past five decades, and approximately, 50-100 million new infections are estimated to occur annually in more than 100 endemic countries. **Objective:** To evaluate the sonographic findings in children with dengue fever (DF) and to determine its role in predicting the severity of the disease. **Methods:** One hundred and twenty dengue serology-positive cases in the age group of 2 months to 18 years were studied. These children were divided into two groups - mild (dengue hemorrhagic fever [DHF] I-II without shock) and severe dengue (DHF III-IV with shock). Sonographic variables of these cases were studied and compared by applying appropriate statistical analysis. **Results:** Out of 120 cases, gallbladder wall thickness (83.3%) and pericholecystic edema (81.6%) were the most common sonographical findings. When sonographic variables of mild and severe groups compared, significant statistical difference was noted in variables such as ascites, pleural effusion, and perinephric edema with p=0.0015, p=0.0058, p<0.000, respectively. **Conclusion:** Ultrasound can be used as an adjunct modality in patients with suspected DF to detect early signs suggestive of the disease and also useful tool to predict severity of the disease.

Key words: *Dengue fever, Epidemic, Serology, Ultrasound*

As per the World Health Organization (WHO), dengue has shown a 30-fold increase globally over the past five decades. Approximately, 50-100 million new infections are estimated to occur annually in more than 100 endemic countries. Every year, hundreds of thousands of severe cases arise resulting in approximately 20,000 deaths [1]. Although the definitive diagnosis of dengue fever (DF) is serological (demonstration of immunoglobulin M [IgM] specific antibodies), the diagnosis of dengue hemorrhagic fever (DHF) is made clinically based on the diagnostic criteria proposed by WHO [1]. There are difficulties in following the WHO criteria in recognizing plasma leakage for diagnosis of DHF. Hemoconcentration (>20%) is usually diagnosed retrospectively and also requires repeated sampling, while hypoproteinemia can be an infrequent finding [2]. Radiographic investigations even though detect effusions, it often requires multiple films to demonstrate the ongoing collections in the pleural cavity which increases the risk of radiation exposure, but ultrasound can detect even smaller amount of pleural effusion and ascites in children with transient plasma leakage and it is highly sensitive. Gallbladder wall thickening (GBWT), i.e., honeycomb pattern on ultrasonography (USG), is the most specific sign that may help in diagnosis and in prognosis of severe dengue infection [3]. USG has been shown to be a useful tool in predicting severe dengue infection at early stage of illness [4]. It is a cheap, safe, rapid and widely available non-invasive imaging method, which can be used to know the presence and degree of plasma leakage at various sites in the body [5]. Hence, we planned this study to evaluate ultrasound findings of DF in children, especially during epidemic, and to assess its role in predicting the severity of disease.

MATERIALS AND METHODS

The present study was a prospective, observational study conducted in the tertiary care pediatric hospital after taking approval from the Institutional Ethics Committee. Children aged between 2 months and 18 years admitted to the tertiary care hospital with confirmed non-structural protein 1 (NS1) Ag/IgM dengue-positive cases were included in this study. Children aged <2 months and >18 years and NS1 Ag/IgM-negative dengue cases are excluded from the study. Purpose of the study was explained to the parents of the study participants and informed consent was taken before the recruitment in the study.

All children with suspected DF (fever of >3 days with thrombocytopenia were subjected to USG during critical phase (3-7 days) of DF, and the time when plasma leakage occurs and the sonographic findings were noted. Then, ultrasound was repeated at the time of discharge. Ultrasound was performed by an experienced radiologist from the radiology department. The other causes of fever such as enteric fever and malaria were ruled out by relevant blood tests. These dengue serology-positive cases were further divided into two groups: Milder group (DHF Grade I-II, i.e., without shock) and severe group (DHF Grade III-IV, i.e., with shock).

Pretested pro forma was used to record relevant information such as patient's data and anthropometry and clinical variables such as fever, nausea/vomiting, abdominal pain, melena, petechiae, central nervous system symptoms (headache, irritability, convulsions), hepatomegaly, splenomegaly, and hypotension were noted and related investigations such as complete hemogram, chest X-ray, liver function tests, ultrasound thorax and abdomen were done. Sonographic variables such as thickened gallbladder wall (>3 mm), pericholecystic fluid, hepatomegaly, splenomegaly, ascites, pleural effusion, perinephric fluid collection were evaluated.

Sonographic variables of both the groups were compared and the p value of each variable was noted. The statistical package used was SPSS version. Qualitative variables such as the presence of various ultrasound features were expressed as percentages. Association of various sonographic features with severity of disease was assessed through Chi-square test of statistical significance. $p \leq 0.05$ was considered for statistical significance.

RESULTS

Total number of suspected cases of DF (i.e., fever with thrombocytopenia) admitted during the study period was 192. Out of these cases, 62.5% (120) cases turned out to be dengue NS1 Ag/IgM positive; therefore, total 120 cases of dengue was studied. Out of which, 88 (73.3%) children belonged to mild and 32 (26.7%) belonged to severe dengue. Out of 120 cases studied, 76 (57%) were male and 44 (43%) were female, with male to female ratio of 1.7:1. Out of 76 male, 56 had mild and 20 had severe dengue, while out of 44 females, 32 had mild and 12 had severe dengue. Out of 120 cases studied, the mean age of presentation in this study was 8.12 years. Age distribution of cases is presented in Table 1.

When signs and symptoms were compared with the severity of dengue, fever was noted in all cases of mild and severe dengue (Table 2). All the signs and symptoms were noted more in severe dengue. Those who presented with hypotension were grouped under severe dengue.

As shown in Table 3, all the three laboratory parameters showed significant difference among mild and severe dengue cases ($p<0.0001$). Among the 120 cases of DF studied, chest X-ray showed pleural effusion in 42 (35%) cases and USG thorax showed pleural effusion in 66 (55%) cases, suggesting higher sensitive of USG thorax than the chest X-ray in identifying the pleural effusion.

Among the 120 cases, GBWT >3 mm was seen in 100 (83.3%) cases. This thickening was seen in all 32 (100%) cases of severe dengue and 68 (77%) cases with mild dengue ($p=0.89$). Pericholecystic edema was seen in 98 (81.6%) out the 120 cases; all 32 (100%) cases of severe dengue and 66 (75%) with mild dengue ($p=0.06$). Ascites was seen in 68 (56%) out of 120 cases; however, significantly, more ($p=0.0015$) cases with severe dengue (32, 100%) had ascites than with mild dengue 36 (40.9%). Similarly, pleural effusion was seen in 66 (55%) out of 120 cases and it was more commonly present in severe dengue group (87.5% vs. 43.18%) than in mild group ($p=0.0058$). 78 (65%) out of 120 cases of DF had hepatomegaly including 22 (68.25%) from severe dengue group and 56 (63.6%) from the mild group ($p=1.000$). Splenomegaly was found in total 36 (30%) cases; out of which 12 (37.5%) were from severe and 24 (27.7%) were from mild group ($p=0.654$). Perinephric edema was seen significantly more cases with severe dengue than with the mild dengue (16 vs. 2) ($p<0.0001$).

Table 1: Age distribution of cases

Age (years)	Total (%)	Mild group (%)	Severe group (%)
<1	4 (3.33)	4	0
1-5	34 (28.33)	26 (29.5)	08 (25)
5-10	48 (40)	38 (43.2)	10 (31.2)
>10	34 (28.33)	20 (22.8)	14 (43.8)

DISCUSSION

Dengue is considered among the most important arthropod-borne viral diseases in humans. Most cases of dengue fever are mild and occur as undifferentiated fever or classic dengue fever. Early recognition and treatment decreases morbidity and mortality [6]. Dengue is the most rapidly spreading mosquito-borne acute febrile viral disease in the world. Epidemics of dengue have hit several Indian cities in the last decade and it remains a health problem with endemicity, both in urban and rural areas, which are infested with *Aedes aegypti* mosquito [7]. The increase in DF cases is due to uncontrolled population growth and urbanization in the absence of appropriate water management, global spread of dengue strains through travel and trade, and inadequate vector control programs [8].

Ultrasound can detect small amount of fluid from body cavities and visceral changes in patients suspected to have DHF. Hence, ultrasound can be used as the first-line imaging modality in patients with suspected DF to detect early signs, suggestive of the disease before serological confirmation of the disease, especially during an epidemic [9]. Colbert et al. in 2007 showed that there is significant correlation of GBWT as measured on ultrasound with both hematocrit and platelet count in severe dengue [10]. Zulkarnain also showed a correlation between elevated hematocrit and the gallbladder thickness [11]. In our study, platelet count, hemoglobin, and hematocrit showed significant difference between mild and severe dengue cases ($p<0.0001$). Hence, decreasing platelet count and increasing hemoglobin and hematocrit can predict the progression from mild to severe dengue.

On USG, GBWT in children with DHF was first reported by Pramuljo and Harun in a study describing sonographic findings in 29 children with severe DHF [12]. Although age-adjusted normal values of GBWT are not well established, the definition of GBWT has generally been accepted to be above 3 mm [13]. In our study, GBWT (>3 mm) was seen in 83.3% of the cases. Chatterjee et al. [7] from Maharashtra reported 83.3% of GBWT while Venkata Sai et al. [8] noted 100% cases with GBWT in their

Table 2: Comparison of clinical features among mild and severe DF

Clinical features	Total (n=120) (%)	Mild dengue (n=88) (%)	Severe dengue (n=32) (%)
Fever	120 (100)	88 (100)	32 (100)
Vomiting	50 (41.6)	34 (38.6)	16 (50)
Abdominal pain	60 (50)	30 (34.1)	30 (93.7)
Melena	60 (50)	36 (40.9)	24 (75)
Petechiae	72 (60)	48 (54.5)	24 (75)
CNS involvement	13 (10.8)	02 (15.3)	13 (84.6)
Hepatomegaly	56 (46.6)	34 (38.6)	22 (68.1)
Splenomegaly	24 (20)	10 (11.4)	14 (43.8)
Hypotension	32 (26.6)	0	32 (100)

CNS: Central nervous system, DF: Dengue fever

Table 3: Comparison of lab parameters among mild and severe DF

Lab parameters	Mean±SD		p
	Mild	Severe	
Platelet	0.684±0.208	0.41±0.12	<0.0001
Hemoglobin	10.693±1.763	13.41±2.82	<0.0001
Hematocrit	33.759±5.091	42.05±2.82	<0.0001

DF: Dengue fever, SD: Standard deviation

study. In the present study, all (100%) cases of severe dengue had GBWT, in comparison to 77% cases with mild dengue (p=0.89). This indicates that GBWT is not a good variable to predict the severity of DF. However, there is considerable association between the severity of dengue infection and GBWT, and its use as an contributory factor in the diagnosis and prognosis in children has been supported by various authors [9,10,14]. A study in Indonesia by Setiawan et al. [15] noted gallbladder thickness in 95% of severe dengue cases and concluded that GBWT is a good indicator to predict severity of dengue which is contrary to our study. In another study done by Mehdi et al. recommended that in an epidemic area, thickened gallbladder wall (<5 mm) with absent Murphy sign can be used as supporting evidence to diagnose DHF [16].

Pericholecystic edema was seen in 81.6% of a total number of cases in our study. Chatterjee et al. from Maharashtra and Venkata Sai et al. from Chennai showed 83.3% and 100% incidence of pericholecystic edema, respectively [7,8]. In our study, pericholecystic edema was seen in all cases (100%) of severe dengue whereas it was present in 75% cases with mild dengue (p=0.06). This indicates that pericholecystic edema is also not a good variable to predict the severity of dengue, but it can support the diagnosis in suspected cases. A similar study in developing countries done by Mehdi et al. in 2012 concluded that pericholecystic edema supports the diagnosis along with other sonographic variables [16]. Venkata Sai et al. found that pericholecystic edema seen in milder form of dengue and not in severe form [8].

In the present study, ascites was seen in 56.6% of the total cases while Venkata Sai et al., Chatterjee et al. and Mia et al. [17] reported 35.2%, 77.08%, and 41% cases of ascites, respectively. In our study, ascites was present in 40.9% of mild and 100% of severe cases (p=0.0015), indicating that ascites is a good sonographic variable in predicting the severity of DF. We found ascites in 100% of the severe cases as ours is tertiary care center and children were referred at the later stage of the disease. Setiawan et al. and Mehdi et al. noted 95% and 60% cases of ascites in severe dengue and 34% and 17.7% cases in mild dengue, respectively. They also concluded that ascites is good indicator to predict the severity of dengue.

Pleural effusion is the most frequent sonographic finding in children in cases of plasma leakage. In the present study, pleural effusion was noted in 55.3% of the total cases similar to that noted in a study done by Chaterjee et al. (45.3%) and Mia et al. (42%); however, Venkata Sai et al. reported much higher incidence (71.8%) of pleural effusion. In our study, significant difference was noted between severe and mild dengue (p=0.005) which indicates that pleural effusion is a good sonographic variable to predict the severity. Setiawan et al. reported 30% cases of pleural effusion in mild dengue and 95% in severe dengue, while Mehdi et al. reported 8.8% cases in mild and 60% in severe dengue. A study by Pramuljo and Harun found pleural effusion in all 29 (100%) severe cases of DF.

Hepatomegaly is a non-specific finding corresponding to the enteric finding of the DF and should be taken into consideration in both clinical and sonographic context of the plasma leakage [5]. In the present study, hepatomegaly was seen in 65% of the total cases, including 63.6% of the mild and 68.25% of the severe dengue cases (p=1.00). Similar observations were noted by various studies with no significant difference between mild and severe dengue, suggesting that it supports the diagnosis rather than predicting the severity. Similarly, splenomegaly was seen in 30% of the total cases in our study including 27.7% of the mild and 37.5% of the severe dengue cases (p=0.65), indicating that it supports the diagnosis with other sonographic variable but did not predict the severity.

Perinephric edema is usually noted on the 4th or 5th day of the illness. The pararenal and perirenal fluid collection may be a sign of severe illness. In the present study, perinephric edema was seen in 15% of the total cases similar to that reported by Mia et al. In our study, significantly, more number of cases with severe dengue had perinephric edema than those with mild dengue (p<0.0001), indicating that it is a significant sonographic variable to predict the severity. Sonographic findings of DF have been described

in several literature. Some authors even concluded that during an epidemic, the ultrasound findings of GBWT with or without polyserositis in a febrile patient should suggest the possibility of DF.

Variation in the sonographic findings in comparison to other studies may be due to the viral virulence, genetic background, immunological responses, and increased pathogenicity of specific serotype. The evidence from different studies show that the pathogenesis of DHF may be multifactorial and the understanding remains incomplete. Furthermore, demographic, economic, behavioral, social factors often play a effective role in disease control [18]. Thus, DF epidemics vary in severity with some epidemics having high mortality rate.

In our study, the incidence of GBWT and pericholecystic edema was more than 80% among total dengue cases studied, suggesting that these along with ascites, and pleural effusion can be used as sonographic markers for early diagnosis of DF during dengue epidemics in clinically suspected dengue cases. Furthermore, sonographic variables such as ascites, pleural effusion, and perinephric edema can predict the severity of DF. Although ultrasound abdomen can detect early signs of disease, for all practical purposes, serology of dengue virus remains gold standard in diagnosing the disease. Serial USG may be required to detect the presence of plasma leakage and other signs of severe dengue; however, we have done it only during critical phase which was a limitation of this study. Second, routine use of USG in resource-limited settings is difficult to apply due to cost factor and logistic limitations.

CONCLUSION

Ultrasound is an important tool for diagnosis and early prediction of the severity of the dengue infection in children. With the support of laboratory parameters, ultrasound abdomen can help predict the progression to severe form of the disease at an early stage. Thus, a simple ultrasound examination may effectively expedite the diagnosis and helps substantially in estimating the severity of the disease.

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