Role Of Ultrasound In Diagnosis And Early Prediction Of Severity Of Dengue Infection In Children

Jeeyani Hetal N*, Parikh Rutvik H, Badiyani Shivam N***, Muliya Harsh J***, Modi Parth A*****

*Associate Professor, ** Assistant Professor, ***Junior Resident, Department Of Pediatrics, GCS Medical College, Hospital And Research Centre-380025

Abstract: Background: Dengue has become a major health problem worldwide. The main objective of the study was to evaluate ultrasound features in children with dengue and determine its role in early diagnosis and predicting the severity of the disease. Material & Methods: 113 serology-positive cases from 1month-14years were divided into three clinical groups – dengue fever, dengue fever with warning signs and severe dengue. Ultrasound was performed during the critical phase and features were analysed. Comparison was done between these groups by applying appropriate statistical analysis. Results: 75(66.3%) were diagnosed as Dengue fever, 16(14.1%) as Dengue with warning signs and 22(19.4%) as Severe dengue. Ultrasound features were, ascites(54,47.7%), gall bladder wall thickening(41,36.28%), pleural effusion(32,28.31%), splenomegaly(28,24.77%) and hepatomegaly(22,19.46%). The ultrasound features like ascites($p<0.05$), pleural effusion($p<0.00001$) and gall bladder wall thickening($p<0.00001$) were significantly higher in Severe Dengue as compared to Dengue fever which suggest that these features predict severity of dengue. Hepatomegaly and splenomegaly showed no significant difference suggesting that it only supports the diagnosis. Conclusion: Ultrasound can be used as an important supportive modality in early diagnosis of suspected dengue. In an epidemic, gall bladder wall thickening, ascites and pleural effusion favours the diagnosis of dengue fever and predicts its severity by identifying plasma leakage.[Jeeyani H Natl J Integr Res Med, 2020; 11(6):22-27]

Key Words: dengue fever, gall bladder wall thickening, ultrasound

Author for correspondence: Dr. Rutvik H Parikh, Department Of Pediatrics, GCS Medical College, Opposite DRM Office, Naroda Road, Ahmedabad– 380025. E-Mail: drrutvikparikh87@gmail.com

Introduction: Dengue is a mosquito-borne acute febrile viral infection caused by the Dengue virus belonging to the family Flaviviridae, transmitted by Aedes aegypti. The incidence of dengue has grown dramatically around the world in recent decades. According to World Health Organization (WHO), 3.9 billion people worldwide are at risk of infection with dengue viruses. The number of dengue cases reported to WHO increased over 8 fold over the last 2 decades, from 5,05,430 cases in 2000, to over 2.4 million in 2010 and 4.2 million in 2019. Despite an existing risk of infection in 129 countries, 70% of the actual burden is in Asia. India is amongst the worst hit countries. Every year, thousands of severe cases arise resulting in deaths[1]. Our state, Gujarat reported 18,219 cases of dengue in 2019 which is the highest number amongst all states[2].

Clinical diagnosis of Dengue can be done on the basis of clinical criteria given by WHO[3]. The definitive diagnosis of dengue fever requires demonstration of non structural antigen (NS1) or Immunoglobulin M (IgM) specific antibodies. There are difficulties in following WHO criteria in recognizing plasma leakage for the diagnosis of severe dengue. Laboratory increase in hematocrit concurrent with rapid decrease in platelet count is one of the warning sign but requires frequent sampling and is often diagnosed retrospectively. Roentgenograms even though detect effusions, often require multiple films to demonstrate ongoing leakage with increased risk of radiation exposure. Whereas, ultrasound can detect even small amount of pleural effusion and ascites in children and poses no added risk. It is a cheap, safe, rapid and widely available non invasive imaging method which can be used to diagnose presence and severity of plasma leakage at various sites in the body[4]. Hence, this study was planned to evaluate ultrasound features of dengue infection in children and assess its role in early diagnosis and prediction of severity of disease.

Material and Methods: The present study was a prospective, observational study conducted in the department of pediatrics in a tertiary care hospital during the dengue epidemic which occurred during July to December, 2019. The study was approved by institutional ethics committee. Written informed consent of the parents was taken before enrolling the children in the study.

Serum samples of all the children less than 14 years admitted in hospital with probable dengue (Live in/travel to dengue endemic area, fever and 2 of the following – nausea/vomiting, rash, aches and pains, tourniquet test positive, leukopenia,

any warning sign) were tested for Dengue NS1/IgM.[5] Children with positive result on serological testing were included in the study. Their demographic and clinical data as well as hematological and biochemical investigations were recorded.

Children were classified into three groups as per clinical classification by WHO- Dengue fever (DF), Dengue fever with warning signs (DFW)(abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement>2 cm, laboratory increase in hematocrit concurrent with rapid fall in platelets) and Severe dengue (SD) (shock, fluid accumulation with respiratory distress, severe bleeding, severe organ involvement)[5].

These children were subjected to ultrasound of chest and abdomen during the critical phase of the course of dengue illness which is day 3 to day 7. Ultrasound was performed by an experienced radiologist from radiology department. Ultrasound features such as ascites, pleural effusion, hepatomegaly, splenomegaly and thickened gall bladder wall (>3 mm) were evaluated.

The statistical package used was MedCalc version 19.5.2. Qualitative variables such as clinical and ultrasound features were expressed as percentages. Association of various ultrasound features with severity of disease was assessed through Chi-square test of statistical significance by comparing each group with other group. Value of $p < 0.05$ was considered as statistically significant and $p < 0.01$ considered highly significant.

Results: During the dengue outbreak, which occurred from the month of July to December in 2019, 134 children were hospitalized with probable dengue out of which 113 children were either Dengue NS1 or IgM positive. Of these, 63 were male (M) and 50 were female (F) with male: female ratio 1.26:1.

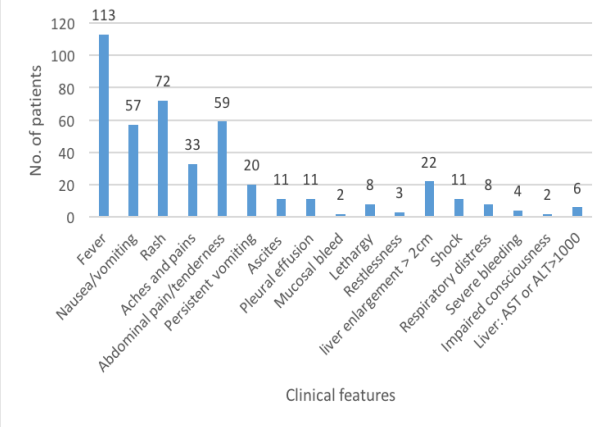
The mean age of presentation was 6.28 years (age range: 1month-14 years). The highest incidence of dengue was seen in 5-10 years (39, 34.51%) followed by 10-14 years (30, 26.54%), 3-5 years (18,15.92%), 1-3 years (14,12.38%) and less than 1 year (12,10.61%). Out of the total 113 children, 75(66.3%) were diagnosed as Dengue fever, 16(14.1%) were diagnosed as dengue fever with warning signs and 22(19.4%) were diagnosed as severe Dengue. (Table 1)

Table 1: Distribution Of Dengue Cases As Per Age Group, Sex And Clinical Diagnosis

Age Group (In Years)	Total Dengue Cases N=113			DF N=75 (66.3%)			DFW N=16 (14.1%)			SD N=22 (19.4%)		
	N (%)	M	F	Total	M	F	Total	M	F	Total	M	F
0-1	12 (10.61)	9	3	7	6	1	1	1	0	4	2	2
1-3	14 (12.38)	7	7	11	5	6	2	1	1	1	1	0
3-5	18 (15.92)	11	7	11	9	2	3	1	2	4	1	3
5-10	39 (34.51)	19	20	31	13	18	4	3	1	4	3	1
10-14	30 (26.54)	17	13	15	10	5	6	3	3	9	4	5
Total	113	63	50	75	43	32	16	9	7	22	11	11

The most common clinical features were, fever in 113(100%), rash in 72(63.71%), abdominal pain in 59(52.21%), vomiting in 57(50.44%) and body ache in 33(29.2%). Warning signs like persistent vomiting were noted in 20(17.69%), ascites in 11(9.7%), pleural effusion in 11(9.7%), mucosal bleed in 2(1.7%), lethargy in 8(7%) and restlessness in 3(2.6%). Severe symptoms like shock was seen in 11(9.7%), severe bleeding in 4(3.5%) and fluid accumulation with respiratory distress was seen in8(7%), impaired consciousness in 2(1.7%) and elevated hepatic enzymes >1000 in 6 (5.3%). (Graph 1)

Graph- 1: Clinical Features In Dengue Fever



Blood investigations demonstrated rising hematocrit in 29(25.6%), leucopenia in 60(53.09%), thrombocytopenia in 78(69%) and transaminitis in 47(41.6%) children. Chi-square test was applied between all the three groups and it was found that all the four parameters were significantly affected in dengue fever with warning signs (p value is 0.038448, p<0.05) and severe dengue (p value is 0.003839, p<0.01) as compared to dengue fever group. (Table 2)

Table 2: Laboratory Parameters In All The Three Clinical Groups Of Dengue Infection

Laboratory Parameters	Total(N=113) N (%)	DF (N=75) N (%)	DFW(N=16) N (%)	SD (N=22) N (%)
Rising Hematocrit	29 (25.66)	9 (12)	7 (43.75)	13 (59)
Leucopenia	60 (53.09)	40 (53.33)	9 (56.25)	11 (50)
Thrombocytopenia	78 (69.02)	52 (69.33)	10 (62.5)	16 (72.27)
Transaminitis	46 (40.7)	21 (28)	11 (68.75)	14 (63.63)

Of the total 113 Dengue cases, 79(69.9%) showed abnormal ultrasound features. Abnormal ultrasound features were seen in 45 out of 75 dengue fever cases (60%), 12 out of 14 dengue fever with warning signs cases (85.7%) and all 22 cases with severe dengue (100%). Ultrasound features were ascites in 54(47.7%), gall bladder wall thickening in 41(36.28%), pleural effusion in 32(28.31%), splenomegaly in 28(24.77%) and hepatomegaly in 22(19.46%) cases. Bilateral, right and left pleural effusion were seen in 16, 13 and 3 cases respectively. The gall bladder wall thickening was seen in 15 of 75 (20%) cases of dengue fever, 9 of 16 (56.25%) cases of dengue with warning signs and 17 of 22 (77.27%) cases of severe dengue. Chi square test was applied between two groups each. As per the test, p value < 0.05 was considered significant and p value < 0.01 was considered highly significant. It is seen that when Chi square test is applied between dengue fever and dengue fever with warning signs, p value is highly significant for pleural effusion and gall bladder wall thickness (GBWT). When it is applied between dengue fever with warning signs and severe dengue, p value is significant only for ascites. Finally, when it is applied between dengue fever and severe dengue, p value is highly significant for ascites, pleural effusion and GBWT. (Table 3)

Table 3: Correlation Between Ultrasound Features And Clinical Severity Of Dengue Infection

Ultrasound Features	Total Cases N=113 (%)	DF N=75 (%)	DFW N=16 (%)	SD N=22 (%)	P Value (Between DF And DFW)	P Value (Between DFW And SD)	P Value (Between DF And SD)
Ascites	54 (47.7)	29 (38.66)	7 (43.75)	18 (81.45)	0.705795	0.014598	0.000369
Pleural Effusion	32 (28.31)	2 (2.66)	11 (68.75)	19 (86.36)	<0.00001	0.188529	<0.00001
Hepatomegaly	22 (19.46)	12 (16)	4 (25)	6 (27.27)	0.390591	0.875179	0.231723
Splenomegaly	28 (24.77)	18 (24)	5 (31.25)	5 (22.72)	0.544646	0.555818	0.901775
GBWT> 3 Mm	41 (36.28)	15 (20)	9 (56.25)	17 (77.27)	0.002815	0.168668	<0.00001

Discussion: It was found that all the age groups in children are affected with dengue but incidence was higher above 5 years of age most probably due to more outdoor activity in children in this age group. Majority of the cases of dengue were mild. Severe dengue was most commonly seen in infancy and 10-14-year age group. The explanation for this is, in infancy there is a phase in which there are decreasing levels of maternally transmitted antibodies. If primary dengue infection occurs in this phase it can be more severe. In adolescent age group, it is more likely that dengue infection may be secondary and hence it is more severe. Various studies have been reported in literature regarding ultrasound features of dengue and correlation of severity of dengue with gall bladder wall thickness in adults but there are very few studies on children.

Ultrasound features express increase in capillary permeability and include cavitary effusions, (ascites, pleural effusion etc.), gall bladder wall thickening and volumetric increase in organs (hepatomegaly, splenomegaly).

Balasubramaniam et al, in his study of comparative analysis of extravasation parameters including clinical signs, hemoconcentration more than 20%, hypoproteinemia, ultrasonography and chest radiography concluded that ultrasonography was the best method for screening dengue hemorrhagic fever with 91.42% sensitivity and negative predictive value of 84.21%. Ascites, Pleural effusion, gall bladder wall thickening and hepatomegaly have been reported by authors as predominant ultrasound features[6].

Gall bladder wall thickening is a non specific finding frequently observed in biliary and non biliary conditions, such as acute cholecystitis, cirrhosis of liver, viral hepatitis, congestive heart failure, chronic kidney disease and hypoalbuminemia on ultrasound examination.

Although the normal value of GBWT is yet to be established, the definition of GBWT has been accepted as > 3mm[7,8]. Gall bladder wall thickening in children with dengue hemorrhagic fever was first reported in 1991 by Pramuljo and Harun in a study describing ultrasound features in 29 children with dengue where 18% showed gall bladder wall thickening[9].

Malleshappa et al and Colbert et al showed that there is significant correlation of GBWT as measured on the ultrasound with both rising hematocrit and falling platelet count in severe dengue[4,10]. Zulkarnain also showed a correlation between elevated hematocrit and GBWT[11]. In our study, it was found that rising hematocrit and thrombocytopenia is significantly more in dengue fever with warning signs and severe dengue as compared to dengue fever group. Hence, GBWT can predict the progression of dengue from mild to severe disease.

In our study, GBWT was found to be 20%, 56.25% and 77.27% in dengue fever, dengue with warning signs and severe dengue, respectively. Chi square test applied between dengue fever and dengue fever with warning signs (p value - 0.002815) as well as severe dengue (p value < 0.00001) for GBWT showed statistically significant p values. We can conclude from this that there is a considerable association between severity of dengue infection and GBWT. Two studies by Setiawan et al from Indonesia have found gall bladder wall thickening in 32-33% cases with mild diseases and 94-95% in severe disease. In the cases of Dengue hemorrhagic fever, GBWT>3 mm and <5mm presents a sensitivity of 93.8% and can be utilized as a criterion for hospitalization. In cases where GBWT > 5mm, the specificity achieves 91.7% threshold that can be used in identifying patients with higher risk of shock[7,8].

Venkata sai et al and Malleshappa et al from India noted gall bladder wall thickening in 100% of their severe dengue patients[4,12]. Mehdi et al recommended that during epidemics thickened gall bladder wall with absent Murphy's sign can be used as a supportive evidence to diagnose Dengue hemorrhagic fever[13]. From the above discussion it can be concluded that although GBWT is a nonspecific finding and may be present in other febrile illnesses, it is useful in early diagnosis, prediction of severity and identifying the patient with higher risk of complications in dengue particularly during an epidemic.

Pleural effusion is the most frequent ultrasound feature in cases of plasma leakage. It may be right unilateral or bilateral. It is rarely left lateral. Similar results are seen in our study. Pleural effusion was present in 8.8%, 62.5% and 77.27% of cases with dengue fever, dengue fever with warning signs and severe dengue respectively.

Chi square test applied between dengue fever and dengue fever with warning sign (p value < 0.00001) as well as severe dengue (p value < 0.00001) for pleural effusion showed statistically significant p values. This indicates that pleural effusion is a good ultrasound feature to predict the severity of dengue. Setiawan et al reported 30% cases of pleural effusion in mild dengue and 95% in severe dengue, while Mehdi reported 8.8% cases in mild and 60% in severe dengue[7,13].

In our study, ascites was present in 38.66%, 43.75% and 81.45% of cases with dengue fever, dengue fever with warning signs and severe dengue respectively. Chi square test applied between dengue fever and severe dengue (p value is 0.000369) as well as dengue fever with warning signs and severe dengue (p value is

0.014598) for pleural effusion showed statistically significant p values. Ascites is also a good indicator to predict severe dengue. Setiawan et al reported 34% cases of ascites in mild dengue and 95% in severe dengue, while Mehdi reported 17.7% cases in mild and 60% in severe dengue[7,13].

Volumetric increase in organs is a non-specific finding and should be taken into consideration in both clinical and sonographic context of plasma leakage. In our study, hepatomegaly was seen in 22(19.46%) cases and splenomegaly in 28(24.77%) cases with no significant difference when Chi square test was applied in between all the three groups.

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.

Our study suggests that, along with GBWT>3 mm, ascites and pleural effusion can be used as ultrasound markers for early diagnosis of dengue fever during dengue epidemics in clinically suspected cases.

Also, these ultrasound features help to predict the severity of the disease. In this study, we have compared ultrasound features between all the three clinical groups of dengue as per latest classification given by WHO.

Ultrasound can detect early signs but serology remains the gold standard for diagnosis. Serial ultrasound may be required to detect plasma leakage, however we have done one ultrasound in critical phase, which is the limitation of the study.

Also, ultrasound may not be readily available in resource limited settings, requires experienced observer and is a costly investigation.

Conclusion: Ultrasound is an important tool for early diagnosis of dengue, besides laboratory tests in acute febrile illness particularly during epidemics. It can help to predict the progression of disease to severe form at an early stage by diagnosing signs of plasma leakage. Thus, a simple ultrasound examination can expedite the diagnosis and help in identification of disease severity.

References:

1. http//www.who.int/news-room/fact-sheets/detail/dengue and severe dengue updated on 23 June 2020. Last accessed on September 30, 2020
2. National vector borne disease control programme, MOHFW, Govt. of India. www.nvbdcp.gov.in updated on September 30, 2020. Last accessed on September 30, 2020
3. World Health Organization, Regional office for South-East Asia. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue heaemorrhagic fever, Revised and Expanded edition. WHO-SEARO 2011. (SEARO Technical Publication series No 60). Geneva: World Health Organization, 2011.
4. Malleshappa K, Srinivasa K. Role of ultrasound in early prediction of severity of dengue infection. Indian J Child Health. 2017;4(2):155-158
5. Parthasarthy A, Kundu R, Yewale V, Kapse A. Textbook of Pediatric Infectious diseases, 2nd edition, New Delhi, Jaypee brothers medical publishers, 2019, Dengue illnesses (Ch. 5.13), p. 348-55
6. Balasubramaniam S, Janakiraman L, Kumar SS, et al. A reappraisal of criteria to diagnose plasma leakage in dengue haemorrhagic fever. Indian Pediatr. 2006; 43:334-9
7. Setiawan MW, Samsi TK, Wulur H, Sugianto D, Pool TN. Dengue haemorrhagic fever: Ultrasound as an aid to predict the severity of disease. Pediatr Radiology. 1998; 28(1):1-4
8. Setiawan MW, Samsi TK, Pool TN et al. Gall bladder wall thickening in dengue haemorrhagic fever: an ultrasonograhic study. J Clin Ultrasound. 1995; 23:357-62
9. Pramuljo HS, Harun SR. Ultrasound findings in dengue haemorrhagic fever. Pediatr Radiology. 1991; 21(2):100-2
10. Colbert JA, Gordon A, Roxelin R, Silva S, Silva J, Rocha C, et al. Ultrasound measurement of gall bladder wall thickening as a diagnostic test and prognostic indicator for severe dengue in pediatric patients. Pediatr Infect Dis J. 2007; 26(9):850-2
11. Zulkarnain I. Gall bladder edema in dengue haemorrhagic fever and its association with hematocrit levels and type of infections. Acta Med Indones. 2004; 36(2):84-6
12. Venkata Sai P M, Dev B, Krishnan R. Role of ultrasound in dengue fever. The British journal of Radiology, 78(2005), 416-418

13.Mehdi SA, Mahais SA, Bhukhari H, Aslam S. Grey scale trans-abdomino-thoracic ultrasonography in evaluation of dengue haemorrhagic fever. APMC.2012; 6:32-6

Conflict of interest: None
Funding: None
Cite this Article as: Jeeyani H, Parikh R, Badiyani S, Muliya H, Modi P. Role Of Ultrasound In Diagnosis And Early Prediction Of Severity Of Dengue Infection In Children. Natl J Integr Res Med 2019; Vol.10(6):22-27