Ultrasound Evaluation of Dengue Fever

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ABSTRACT
This study is to determine whether ultrasound is an important adjuvant to clinical and laboratory profile: to predict prognosis and assessing severity of disease with platelet correlation. Ultrasonic variations seen in various age groups were studied. We conducted a prospective study in serologically positive 115 cases of dengue fever between June and December 2015 were refered for USG abdomen and USG thorax.

KEYWORDS: Dengue fever, ultrasound, ascities, gall bladder odema, pleural effusion.

INTRODUCTION
Dengue infections caused by the four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, DENV4) of the family Flaviviridae are the most important arboviral diseases in humans, in terms of geographical distribution, morbidity and mortality. It is transmitted by mosquito aedes aegypti. Dengue virus infections can cause a wide clinical spectrum of disease, from a mild febrile illness known as ‘dengue fever’ through to ‘severe dengue’, previously known as dengue haemorrhagic fever (DHF), which is characterized by capillary leakage leading to hypovolaemic shock, organ impairment and bleeding complications (1,2). Clinically dengue manifests with sudden onset of high fever with chills, intense headache, muscle and joint pain, severe backache(3). Hemorrhagic diathesis and thrombocytopenia with concurrent hemoconcentration are a constant finding. The aim and objectives of the study is to determine the ultrasound findings in Dengue fever patients and their proportions. This study was performed to find whether ultrasound is an important adjunct to clinical and laboratory profile in diagnosing dengue fever. Ultrasonography (USG) is a cheap, rapid and widely available non-invasive imaging method(4,5). To further determine whether ultrasound is useful in predicting the severity of disease.

MATERIALS AND METHODS
Present prospective study was conducted at Mamata General Hospital; all dengue serology positive cases referred by the Department of General medicine and pediatrics to the Department of Radio diagnosis in Mamata
General Hospital, Khammam from June 2015-Dec 2015. A total of 115 cases suspecting dengue, based on clinical (fever, body aches, bleeding manifestations) and laboratory profile (platelet count) will be subjected to Ultrasonography. The study was conducted using Esaote MyLab 60 and SonoScape machines. TAS examinations were carried out using curvilinear 3.5 to 5-MHz transducers. Gallbladder wall thickening was measured by placing the calipers between the two layers of anterior wall. Liver measuring more than 15cms was taken as hepatomegaly and spleen more than 12 cms was considered as splenomegaly \(^{(6)}\). Thoracic scanning was done in sitting or supine posture. Both the pleural spaces were evaluated through an intercostal approach.

**Inclusion criteria:**
Patients of all age groups with dengue serological markers (Ns1Ag, IgM antibody, IgG antibody) positive cases

**Exclusion criteria:**
- All other fever cases (other than dengue)
- Serologically negative dengue cases
- Other conditions which predisposes to thrombocytopenia
- All other causes which predisposes to hepatosplenomegaly
- All other causes which predisposes to ascitis, POD collection & pleural effusion.
- Causes of cholecystitis (calculous and other causes of acalculous)
- HELLP syndrome, which occurs in pregnant women with pre-eclampsia and eclampsia

**Statistical analysis:**
All the data will be recorded in the proforma of the individual patients. At the end of the study, these data will be analyzed and from the results, relevant statistical data will be obtained. Total 115 seropositive cases are again dived into four groups based on their age to determine the age distribution of imaging features. Group 1 consists of patients from 0 to 20 years (41 patients), group 2 between 21 to 40 years (44 patients), group 3 between 41 to 60 years (27 patients) and group 4 above the age of 60 years (3 patients).

**RESULTS**
Out of 115 cases 33 had Hepatomegaly (47%) figure1, 25 had Ascitis (35.7%) figure2, 18 had Cholecystitiys (25.7) figure3, 13 had Spleenomegaly (18.6%), 11 had Bilateral Pleural effusion (15.7%), 8 had Right sided Pleural effusion (11.4%), 5 had POD collection (7.1%), 4 had Hydronephrosis (5.7%), 3 had Left sided Pleural effusion (4.2%) and 48 cases has no abnormal ultrasound findings (41.7%) table1. 22 Cases with platelet count >1,50,000 shows normal ultrasound features in 16 cases (72.2%), hepatomegaly in 4 cases (18.2%), ascitis in 1 case (4.5%) and bilateral pleural effusion in 1 case (4.5%). 57 cases with platelet count between 75,000 to 1,50,000 shows normal ultrasound features in 21 cases (36.8%), hepatomegaly in 17 cases (29.8%), splenomegaly in 8 cases (14%), ascitis in 9 cases (15.7%), cholecystitis in 9 cases (15.7%), POD collection in 3 cases (5.2%), bilateral pleural effusion in 5 cases (8.7%) and right sided pleural effusion in 5 cases (8.7%). 16 cases with platelet count between 50,000 to 75,000 shows normal ultrasound features in 3 cases (18.7%), hepatomegaly in 6 cases (37.5%), splenomegaly in 1 case (6.2%), ascitis in 5 cases (31.2%), cholecystitis in 4 cases (25%), POD collection in 1 case (6.2%), bilateral pleural effusion in 2 cases (12.5%), right sided pleural effusion in 2 cases (12.5%) and left sided pleural effusion in 2 cases (12.5%). 20 cases with platelet count <50,000 shows normal ultrasound features in 5 cases (25%), hepatomegaly in 6 cases (30%), splenomegaly in 4 cases (20%), ascitis in 10 cases (50%), cholecystitis in 5 cases (25%), POD collection in 1 case (5%), bilateral pleural effusion in 4 cases (20%), right sided pleural effusion in 1 case (5%) and left side pleural effusion in 1 case (5%) table2.
**Figure 1:** 28 yrs male patient with dengue fever shows mild hepatomegaly.

**Figure 2:** 33 years female patient with dengue fever shows Ascitis

**Figure 3:** Ultrasound liver through right hypochondrium shows thick wall gall bladder with minimal pericholecystic fluid.

**TABLE 1:** Ultrasound features in our study

| FINDING       | NUMBER OF CASES |
|---------------|-----------------|
| Hepatomegaly  | 33(47.1)        |
| Spleenomegaly | 13(18.6)        |
| Ascitis       | 25(35.7)        |
| Cholecystitis | 18(25.7)        |
| POD collection| 5(7.1)          |
| Bilateral pleural effusion | 1(15.7)        |
| Right pleural effusion | 8(11.4)        |
| Left pleural effusion | 3(4.2)         |
| Hydronephrosis | 4(5.7)          |
| Total number of cases | 70             |

**TABLE 2:** Clinical Findings In Corelation With Platelet Count.

| Platelet Count | Total number of cases | Normal | Hepatomegaly | Spleenomegaly | Ascites | Cholecystitis | POD Collection | Bilateral pleural effusion | Right pleural effusion only | Left pleural effusion |
|----------------|-----------------------|--------|--------------|---------------|---------|--------------|-----------------|---------------------------|--------------------------|------------------------|
| >1,50,000      | 22                    | 16(72.2) | 4(18.2)      | 0             | 1(4.5)  | 0            | 0               | 1(4.5)                    | 0                        | 0                      |
| 75,000 - 1,50,000 | 57               | 21(36.8) | 17(29.8)     | 8(14)         | 9(15.7) | 9(15.7)      | 3(5.2)         | 5(8.7)                    | 5(8.7)                   | 0                      |
| 50,000 – 75,000 | 16                 | 3(18.7)  | 6(37.5)      | 1(6.2)        | 5(31.2) | 4(25)        | 1(6.2)         | 2(12.5)                   | 2(12.5)                   | 2(12.5)                |
| <50,000        | 20                  | 5(25)    | 6(30)        | 4(20)         | 10(50)  | 5(25)        | 1(5)           | 4(20)                    | 1(5)                     | 1(5)                   |

**TABLE 3:** Incidence Of Sonographic Findings In Relation To Different Age Groups

| Age          | Total number of Cases | Normal | Hepatomegaly | Spleenomegaly | Ascites | Cholecystitis | POD collection | Bilateral pleural effusion | Right pleural effusion only | Left pleural effusion |
|--------------|-----------------------|--------|--------------|---------------|---------|--------------|-----------------|---------------------------|--------------------------|-----------------------|
| 0-20         | 41                    | 15(36.5) | 10(24.4)    | 3(7.3)        | 15(36.5) | 10(24.4)     | 2(4.8)         | 6(14.6)                   | 5(12.1)                  | 1(2.4)                |
| 21-40        | 44                    | 19(43.1) | 11(26.8)    | 8(18.2)       | 8(18.2) | 7(15.9)      | 4(9.1)         | 5(10.4)                   | 2(4.5)                   | 1(2.3)                |
| 41-60        | 27                    | 12(44.4) | 11(40.7)    | 2(7.4)        | 2(7.4) | 1(3.7)       | 0               | 0                         | 1(3.7)                   | 1(3.7)                |
| 61-80        | 3                     | 2(66.6)  | 1(33.3)     | 0             | 0       | 0            | 0               | 0                         | 0                        | 0                     |
The findings regarding age distribution of imaging are:

- Hepatomegaly is common in group 3 than other groups.
- Spleenomegaly is common in group 2.
- Ascitis and cholecystitis are common in group 1 than other age groups.

Combination of imaging features:

- Ascitis, Cholecystitis and Bilateral pleural effusion are more common in group 1.

Correlation with platelet count:

- Cholecystitis is seen more common in patients with platelet count less than 50,000 (25%), and also between 50,000 to 75,000 (25%).
- Ascitis (50%), Bilateral pleural effusion (20%) and spleenomegaly (20%) are most commonly seen in patients with platelet count less than 50,000.
- Hepatomegaly (37.5%) is more commonly seen in patients with platelet count between 50,000 to 75,000.

DISCUSSION

The name dengue originated from the Swahili word for “bonebreaking fever” or the word for “the walk of a dandie” in Spanish. The first probable case of dengue fever (DF) was recorded during the Jin Dynasty (265–420 AD) in China. The first recognized epidemics occurred almost simultaneously in Asia, Africa and North America in the 1780s, shortly after the identification and naming of the disease in 1779 by Benjamin Rush (7). The incidence of dengue has grown dramatically around the world in recent decades. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) (8). Presently, about 40% of the world’s population is at risk and there are 50–100 million cases every year. An estimated 500 000 people with severe dengue require hospitalization each year and about 2.5% of those affected die (9). In India, dengue is widespread and endemic in most major cities (10). Dengue virus is transmitted from human to human by different species of Aedes mosquitoes. The strong association between the development of severe disease in secondary dengue and the observation that complications occur when the viraemia is in steep decline, has led to the suggestion that the pathogenesis of severe dengue is immune-mediated. Halstead in the 1970s proposed the ‘antibody-dependent immune enhancement theory’ (ADE) based on in vitro and primate studies (11). This association of sequential dengue infections being a risk factor for severity has been confirmed repeatedly in epidemiological studies, from different parts of the world (12,13). In addition, a particular sequence of infecting serotypes have been linked to severe disease, with several studies suggesting severe dengue is more common in a secondary infection with DENV2 (14,15). During the second infection with a different dengue serotype, pre-existing antibody from the first infection fails to neutralize and may instead enhance viral uptake and replication in mononuclear cells (16). The resulting higher viral load has been linked to disease severity (17). Other factors that may contribute to the pathogenesis of severe dengue include more virulent strains of the virus (18), host genetic factors, age and comorbidities (19-21).

Significant changes are found in major organ systems (22)

1. Vascular changes include vasodilatation, congestion, perivascular haemorrhage and oedema of arterial walls
2. Proliferation of reticuloendothelial cells with accelerated phagocytic activity is observed frequently
3. The lymphoid tissues show increasing activity of the B lymphocyte system with active proliferation of plasma cells and lymphoblastoid cells
4. In the liver there is focal necrosis of the hepatic and Kupffer cells, with formation of Councilman-like bodies.

5. Dengue virus antigen is found predominantly in cells of the spleen, thymus and lymph nodes, in Kupffer cells and in the sinusoidal lining cells of liver and alveolar lining cells of the lung.

The pathophysiological hallmarks of severe dengue are plasma leakage and abnormal haemostasis. Clinical evidence supporting plasma leakage includes a rapid rise in haematocrit, hypoproteinaemia, pleural effusions and ascites and reduced plasma volume, leading to haemodynamic compromise and hypovolaemic shock. Age-related changes occur in microvascular permeability, with children having higher filtration capacity than adults, which would explain why dengue shock syndrome is more common in childhood (23).

Warning Signs (2009 WHO GUIDE LINES)

1. Abdominal pain or tenderness
2. Persistent vomiting
3. Clinical fluid accumulation
4. Mucosal bleed
5. Lethargy/restlessness
6. Liver enlargement >2 cm
7. Laboratory increase in HCT concurrent with rapid decrease in platelet count

Early diagnosis of dengue virus (DENV) infection can improve clinical outcomes by ensuring close follow-up, initiating appropriate supportive therapies and raising awareness to the potential of hemorrhage or shock. Serology is the mainstay in the diagnosis of DF, positive serology (anti-dengue antibody) is the mainstay in the diagnosis of DF. Haemagglutination inhibition antibodies usually appear at detectable level by day 5 to 6 of febrile illness. Non-structural glycoprotein-1 (NS1) has proven to be a useful biomarker for early diagnosis of dengue (24). The acquired immune response following a dengue infection consists of the production of IgM and IgG antibodies primarily directed against the virus envelope proteins. Ultrasound abdomen and horax findings in early, milder form of dengue fever include GB wall thickening, minimal ascites, pleural effusion and hepatosplenomegaly. Severe forms of the disease are associated with the collection of fluid in the perirenal and paranrenal regions, hepatic and splenic subcapsular fluid, pericardial effusion, pancreatic enlargement and hepatosplenomegaly. Due to intraparenchymal and sub capsular hemorrhages, there will be an alteration in the normal liver echo texture (25, 26).

However, in our study, we did not find any of the above-mentioned sonographic features even in severe forms of dengue fever except hepatosplenomegaly. GB wall thickening also occurs in association with other conditions such as ascites, hypoalbuminemia, congestive cholecystopathy and in patients with cirrhosis of liver and portal hypertension. It is a very non-specific finding when considered in isolation and is therefore a major limitation of this study. Imaging features of dengue fever such as GB wall thickening, ascites, pleural effusion, hepatomegaly and splenomegaly are reasonably accurate in the diagnosis of dengue fever. This helps in starting appropriate management of the patient as soon as ultrasound is done, especially in centers where high end laboratory facilities may not be available for serological confirmation. While serological tests are confirmatory in the diagnosis of dengue fever, ultrasound can be of value in the assessment of severity. In a similar study conducted in 2012 by Santosh et al., the most common age group affected is 21-40 years like in our study table 3. In that study edematous GB wall thickening was the most common finding (66.7%) but in our study hepatomegaly is the most common finding (47.1%). In their study ascitis is seen in 64.5% but in our study it is seen in 35.7% and is the second most common finding. The severity is related to platelet count where more than three abnormal sonographic features are seen when count is less than 40,000.
CONCLUSION
Ultrasound features like cholecystitis, ascitis, pleural effusion (bilateral or right sided), hepatomegaly, and spleenomegaly strongly favor the diagnosis of dengue fever. Sonographic features are also helpful in estimating the severity. The degree of thrombocytopenia shows a direct relationship to abnormal sonographic features.

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