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Role of Ultrasonography ("Honeycomb Sign") in Early Detection of Dengue Hemorrhagic Fever

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Abstract

Aim: This study was conducted to evaluate the early, specific ultrasonographic (USG) findings in clinically suspected dengue hemorrhagic fever (DHF) along with its prognostic value.

Methods: From May 2009 to June 2012, 20 patients were referred with high-grade fever and abdominal pain. All the patients underwent immediate abdominal USG. A specific change – "Honeycomb" pattern in the thickened gallbladder (GB) wall (mostly in the fundal area) – on USG suggested the diagnosis of DHF, which was subsequently confirmed by serology in all patients. Treatment was stated on the bases of USG findings before the positive serology report. After starting treatment the USG on the 3rd day showed reduction in GB wall thickening, which was almost cleared by the 7th day in clinically improving patients.

Results: All 20 patients had type-2 dengue fever, i.e., DHF Grades I and II, as confirmed after USG by platelet count and serologic tests. USG features included a much-thickened GB wall in all the patients, but showing a "Honeycomb" pattern (proposed as Sachar and Sunder's sign) in 19 patients (95%), multilayered (laminated/onion peel) in 1 patient (5%), ascites in 15 patients (75%), splenomegaly in 8 patients (40%), and pleural effusion in 14 patients (70%). (Pleural effusion was either right-sided or bilateral, but never alone on the left side.)

Conclusions: Abdominal emergency USG can be used as a first-line imaging modality in patients with suspected DHF to detect early signs that are suggestive of the disease prior to obtaining serologic confirmation test results, especially in a dengue fever epidemic area. Also, reducing GB wall thickness can be used as a prognostic sign in cases of DHF.

Key Words: *Ultrasonography, dengue haemorrhagic fever, gall bladder wall thickening, honeycomb* sign

Introduction

Dengue fever (DF), also known as break bone fever, is a tropical communicable disease. It is an acute mosquito-transmitted systemic viral disease caused by 1 of 4 virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). It is most often due to serotype 2, and less often to serotypes 3, 4 and 1 (in decreasing order of frequency) of the genus Flavivirus. It is the most common worldwide arboviral disease. The disease is transmitted from human to human by a bite of a female anopheles mosquito, Aedes aegypti. DF is endemic in South East Asia, East and West Africa, the West Indies, the Pacific Islands, the Caribbean, Mexico, and Central America. In India many outbreaks of DF have been reported from the Delhi-

NCR region, Chennai and Maharashtra. DF occurs only in the active mosquito season (warm weather). USG is useful as a first-line diagnostic modality for the prediction of DHF [1]. A thickened GB wall showing a "Honeycomb" pattern is almost a specific USG sign that may help in the early diagnosis, as well as in the prognosis, of DHF. The early abdominal USG finding of a diffusely much-thickened GB wall with a "Honeycomb pattern" in adult patients with DHF has never been described in the past. However, there is only one published report of GB wall thickening with a transient reticular pattern [2]. We conducted a prospective study of 20 patients of suspected DHF in an attempt to identify early, specific USG features of DHF.

Material and Method

From May 2009 to June 2012, 20 patients clinically suspected of having DHF were referred for emergency USG. The clinical manifestations included the sudden onset of high fever, chills, frontal headache, retroocular pain, muscle and joint pain, sore throat, nausea, vomiting, and right upper abdominal pain. Some patients had prostration and depression. All 20 patients underwent urgent abdominal USG at admission. A much-thickened GB wall showing a "Honeycomb" pattern (Sachar and Sunder's sign) was defined as a confirmatory sign of DHF in 95% of cases (Figure 1 and Figure 2). Such a unique pattern of GB wall thickening has never been reported in literature (so far). In the remaining 5% of cases, a laminated/onion-peel/multilayered diffuse GB wall thickening pattern was observed (Figure 3). Other varieties of GB wall thickness, like a transient reticular pattern, have been reported by a few authors [2]. The splenic volumetric index was calculated from the distances from the hilum to the lower tip of the spleen and from the hilum to the upper tip of the spleen. A splenic index greater than 20 cm was defined as splenomegaly [3,4], but we defined splenomegaly when the splenic index was greater than 15 cm. The presence of ascites and pleural effusion were also confirmed during the USG. Before inclusion in the study, verbal informed consent to participate was taken from all patients. Treatment was started in all patients based on USG findings.

After initial emergency USG, all patients underwent serology testing for confirmation of DF. Positive serology is defined as a 4-fold or greater change in re-

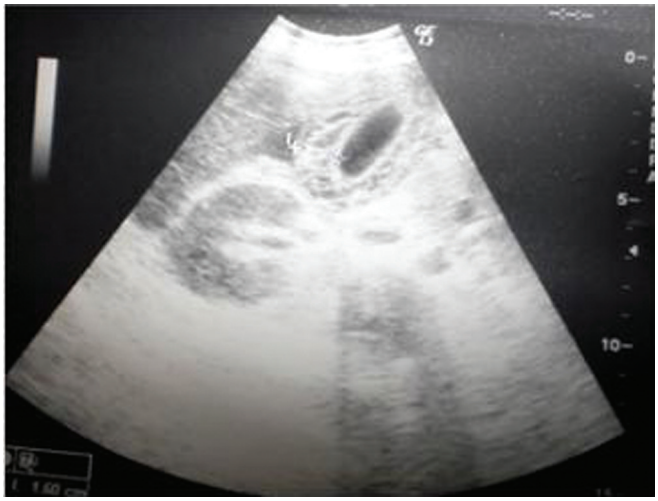

Figure 1. Showing a Honeycomb pattern of gall bladder wall thickening (GBWT) in dengue hemorrhagic fever (DHF) – Sachar and Sunder's sign.

Figure 2. Showing a Honeycomb pattern of gall bladder wall thickening (GBWT) in the fundal region in dengue hemorrhagic fever (DHF) (second case, 1st day).

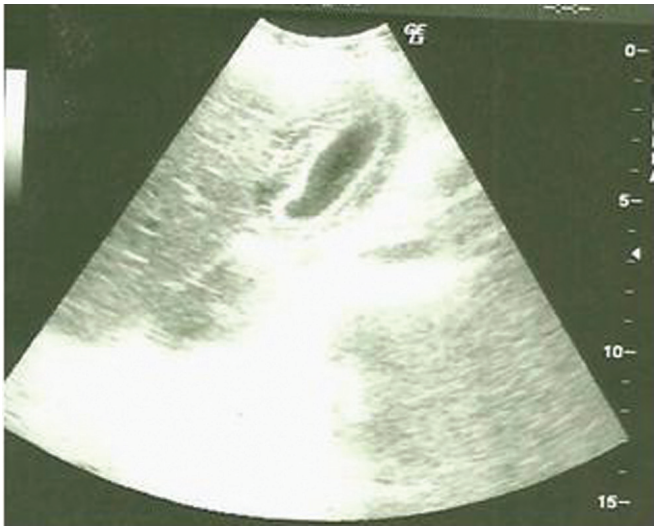

Figure 3. Showing diffuse laminated gall bladder wall thickening (GBWT) in dengue hemorrhagic fever (DHF).

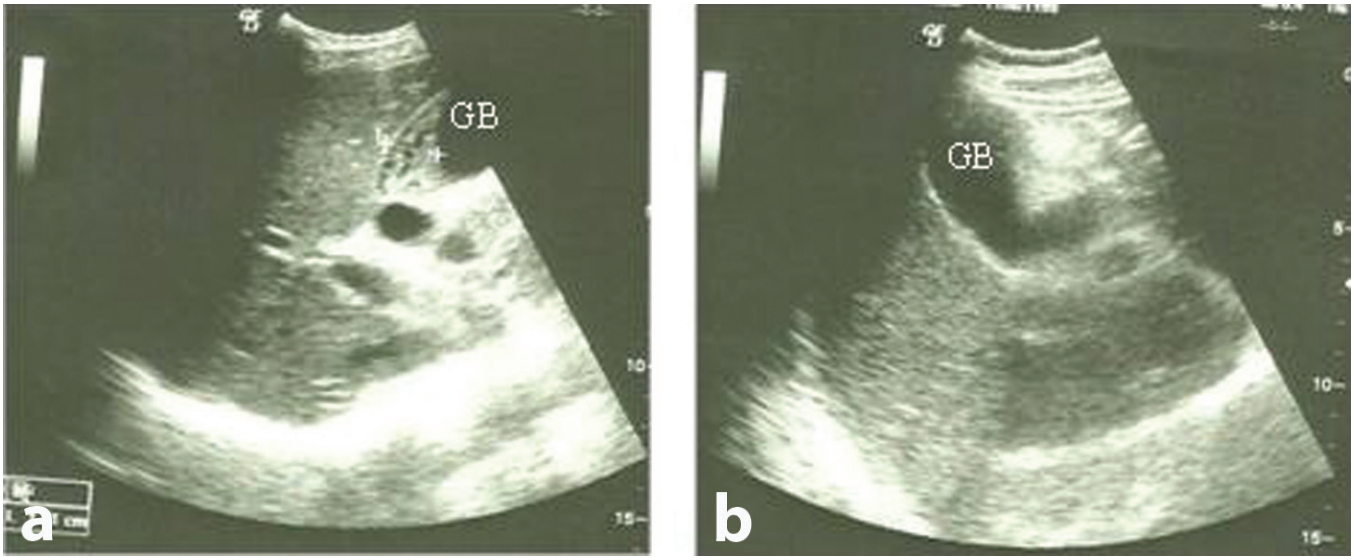

Figure 4. Showing resolving gall bladder wall thickening (GBWT) on 3rd (a) and 7th (b) days in the second case.

ciprocal IgG antibody titers to 1 or more dengue virus antigen in paired serum samples or a positive IgM antibody test on a late acute phase or convalescent-phase serum specimen by an enzyme-linked immunosorbent assay. Serology was positive in all the 20 patients.

After initiation of treatment in the form of prompt fresh blood transfusion, preferably packed cells, fresh platelet concentrate, maintaining correct fluid and electrolyte balance, and steroids, all patients underwent subsequent USG on the 3rd and 7th days. In all clinically improving cases, GB wall thickening was reduced by the 3rd day, and almost disappeared by the 7th day (Figure 4a,b).

Results

Among the 20 patients aged between 20 and 60 years with suspected DHF, 4 were women (one pregnant) and 16 were men. All patients had high-grade fever, but only 10 patients also had chills. All the 20 patients had abdominal discomfort/upper abdominal pain. The most common emergency USG finding was a "Honeycomb-type" thickened GB wall in 19 patients (95%). The onion peel/laminated/multilayered GB wall thickening pattern was seen in 1 patient only (5%). The GB wall thickness ranged between 6 and 12 mm. Ascites was noted in 15 patients (75%). A thickened GB wall was more common in patients with ascites. 8 patients (40%) had splenomegaly, and 14 patients (70%) had pleural effusion. Right-sided pleural effusion was observed in 10 patients (50%), and 4 patients had bilateral pleural effusion (20%). There was no mortality in these DHF patients, and all were managed successfully.

We observed that in all clinically improving cases, GB wall thickening (Honeycomb or onion-peel/laminated pattern) was reduced gradually, almost clearing on the 7th day after initiation of the treatment.

Discussion

DHF has been a major health problem with an incidence of 11.56/100,000 people and a mortality of about 2.7%. DF is endemic in many tropical and subtropical regions, like Southeast Asia (including India). DF is an acute febrile illness characterized by the sudden onset of high fever, chills, frontal headache, sore throat, retroocular pain, muscle and joint pain, nausea, vomiting, and rash [5,6]. Laboratory findings commonly associated with DF include neutropenia, lymphocytosis, increased concentration of liver enzymes [7], and thrombocytopenia. Usually, the diagnosis of DF is suspected on the basis of clinical manifestations and laboratory results. The presumptive diagnosis of DF can be confirmed by serologic detection of the virus, antiviral antibodies or virus culture from a blood sample in the acute phase, but the results are often obtained too late to be of clinical benefit. Therefore, additional diagnostic modalities for use in emergent, first-line evaluation of suspected DF patients are being increasingly sought. Although not specific, the USG findings in DF are obtained more rapidly than the results of serologic tests. The early USG findings of DF have been reported in the literature, with the incidence

of GB wall thickening being 33% in mild cases and 94% in severe cases [1], as in our study. GB wall thickening of more than 5 mm could be adopted as a criterion for identifying DHF patients at high risk of developing hypovolaemic shock (dengue shock syndrome (DSS)) with a specificity of 92% [1].

We report a special type of "Honeycomb" thickening of the gallbladder wall (mostly in the fundal region) which has never been reported in literature (so far). It seems to be almost specific for diagnosing DHF. Only Oliveira GA et al. have reported about transient reticular GB wall thickening in severe DF due to plasma leakage in the wall [2]. Tai et al. [8] found that USG findings of DF were a thickened GB wall, ascites, splenomegaly, and pleural effusion, which were present in our study also. Bhamarapravati et al. [9] also found edema of the serosa of the GB and ascites in the peritoneal cavity in patients with DF. A fluid collection limited to the left pleural cavity has never been reported [10].

The pathophysiology of DF is that the virus especially attacks the capillary endothelium, resulting in increased permeability and causing plasma leakage and serous effusion with a high protein content (mostly albumin) [11]. Immune complexes are deposited on capillary endothelium, causing further damage by increasing capillary fragility that can be shown by a positive tourniquet test.

When DF is combined with right upper quadrant pain, the differential diagnosis includes acute acalculous cholecystitis [12,13]. In cases of acalculous cholecystitis, GB is always distended with mild thickening of the wall with visible stratification along with a rim of fluid around the GB. There are different USG findings between gangrenous cholecystitis and the thickening of the GB wall in DHF; in the latter the GB wall is much more evenly thickened with a Honeycomb pattern than that in gangrenous cholecystitis. In gangrenous cholecystitis, there is a sloughed membrane appearing as a linear intra-luminal echo. In cases of acute cholecystitis with stones, classic appearance is mild GB wall thickening with distended GB having luminal stone ± sludge. In more advanced cases of acute cholecystitis, marked diffuse thickening of the GB wall with stratification (as in generalized edematous states) is seen, and multifocal non-contiguous hypoechoic pockets of edema fluid within the thickened GB wall are commonly seen. A thin rim of fluid (edema) is often seen around much of the GB wall. In xathogranulomatous cholecystitis, there is irregular diffuse or focal gallbladder wall thickening usually associated with stones. There may be a hyperechogenic band or nodule or pericholecystic fluid collection around the gallbladder in a few cases [14]. In adenomyomatosis of the gallbladder, there is diffuse or segmental gallbladder wall thickening with intramural diverticulas. Diverticula containing bile are anechoic; those with stones or sludge are hyperechoic, with or without shadowing [15].

A diffuse gall bladder wall thickening (GBWT) is not specific for primary GB disease. Several USG studies have reported GBWT of more than 3 mm with various non-biliary conditions, including ascites, hypoalbuminemia, portal venous hypertension, end-stage cirrhosis, various types of hepatitis, pancreatitis, chronic heart failure, and renal insufficiency [16, 17, 18]. But the character of GBWT is different in these diseases. As in acute viral hepatitis, there is marked circumferential sympathetic GBWT, but the lumen is not distended and periportal cuffing is seen in portal venous radicals in the liver, which is not the case in acute cholecystitis or DF.

There is a considerable association between GBWT and the severity of DF [1]. Dengue virus induces GBWT, ascites, and pleural effusion, which may be related to the inflammation of the liver and spleen. The formation of ascites and pleural effusion could also be due to an increase in capillary permeability that occurs subsequent to an increase in chemotaxic factors shed by inflammatory cells and endothelial damage caused by the dengue virus [19]. Thulkar et al. [20] reported USG findings in 40 patients with DHF, including pleural effusion, ascites, and GB wall thickening. (Splenomegaly was not cited.) In our series, the incidence of splenomegaly was 40% on USG.

Conclusion

In a DF endemic area, when USG shows a thickened GB wall having a Honeycomb pattern (Sachar and Sunder's sign), ascites, splenomegaly, and pleural effusion, in a febrile patient, DHF should be considered in the differential diagnosis until it is proven otherwise. On USG, GBWT can be diagnostic as well as prognostic.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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