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Systematic Review

Role of Ultrasonography in The Diagnosis of Dengue Fever: A Systematic Review

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ABSTRACT

Dengue fever (DF) is a complex virus-borne febrile disease with a wide spectrum of clinical manifestations **Objective:** To review the literature and outlining the role of abdominal and chest ultrasonography in the diagnosis and as a predictor of severity of dengue fever. **Methods:** Standard medical electronic databases were searched and relevant articles were used to present the conclusive outcomes. **Results:** Eighteen studies on 2601 patients undergoing chest and abdominal ultrasonography fulfilled the inclusion criteria. The incidence of plasma leakage triad such as pleural effusion, ascites and gallbladder wall thickening was 44.98 %, 39.44 % and 61.89 % respectively. Other ultrasonic findings included Hepatomegaly, splenomegaly and pericardial effusion. **Conclusion:** In patients with suspected DF and dengue hemorrhagic fever, the abdominal and chest ultrasonography, although nonspecific, may be a relevant ancillary tool for the early diagnosis of microvasculature hyper-permeability in addition to a tool used for the prediction of disease severity identifying mild and severe cases of DF. Furthermore, ultrasonography may also be used for the differential diagnosis of other febrile conditions affecting both pediatric and adult population.

INTRODUCTION

Dengue fever (DF) is a vector borne disease where the majority of the victims experience a sudden onset of fever [1-4] associated with the constitutional features of viral illness like lethargy, weakness, myalgia, arthralgia, anorexia, sore throat, headaches, and a macular skin rash [4-13]. The major arthropod vector for transmission of the dengue viruses is Aedes aegypti mosquito [14-19]. The human response to DF virus infection in the 20th century has been reported in several studies mainly on the outcomes of adult volunteers [1-9]. DF was found to be a new clinical syndrome, an acute febrile disease accompanied by a complex of physiologic abnormalities affecting multiple organ systems including the liver, blood coagulation, complement, hematopoiesis, serum proteins, and the vascular system that reach maximal expression at excessive permeation [12-17]. Due to significant impact on the permeability of microvasculature throughout human body, the DF may also be called as the dengue vascular permeability syndrome (DVPS). The DVPS provides a basic principles of ultrasonography related findings in the patients with DF. The diagnostic modalities for DF are clinical picture denoting hemorrhagic fever, Thrombocytopenia, Mosquito inoculation for virus isolation, Viral RNA detection by PCR, Dengue antigen detection, Dengue antibody detection, Dengue neutralizing antibody detection, combined antigen-antibody detection [19]. Polyserositis is mainly cause by the hemorrhagic manifestations as well as the thrombocytopenia of severe DF. In the medical literature it was established that, the hypotension secondary to the excessive leakage of plasma through the serosal surfaces may occurs up to 48 hours after (Fever abatement) defervescence [20]. Main

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objective of this systematic review is to highlight major ultrasonographic features and assessing its role in the evaluation of DF.

METHODS

Data sources and Search strategy: All published articles on the diagnostic, prognostic, follow-up, and complication detection role of ultrasonography of chest, heart, abdomen and pelvis were identified through searches of standard medical electronic databases of MEDLINE, EMBASE, CINAHL, Cochrane library, grey literature and PubMed. The search terms "dengue fever", "dengue hemorrhagic fever", "dengue fever syndrome", "dengue vascular permeability syndrome", "dengue fever hemorrhagic pathy", "dengue fever thrombocytopenia" and "dengue fever abdominal syndrome" were used in combination with the medical subject headings "ultrasound", "ultrasonography", "abdominal imaging", "chest ultrasonography", and "pelvic ultrasonography". . All abstracts, case reports, case series and published single center or multicenter audits were retrieved and searched comprehensively. There were no restrictions on the review of studies in terms of age, gender, origin, language and number of patients reported. A flow chart of the literature search is shown in Figure 1. All types of randomized controlled trials, non-randomized controlled trials and comparative studies evaluating the role of ultrasound in depicting the plasma leakage related chest, abdomen and pelvic findings, Case series reporting the data of 10 or more patients, comparative studies reporting the role of ultrasound in defining severity of DF, published studies reporting the diagnostic accuracy of the ultrasonography for DF were included.

Data synthesis and statistical analysis: Data was collected in the tabulated form, summated outcome was presented as mean calculated using the Microsoft Excel spread sheet and data analysis tool.

RESULTS

Eighteen studies on 2601 patients reported the plasma leakage related ultrasonic findings in patients with DF. The incidence of plasma leakage triad such as pleural effusion, ascites and gallbladder wall thickening was 44.98 %, 39.44 % and 61.89 % respectively. Other ultrasonic findings included Hepatomegaly, splenomegaly, pericardial effusion and peri-cholecystic fluid collection. The comprehensive data on chest and abdominal imaging by ultrasonography are given in Table 1 and Figure 1. Ascites is the second major indicator of plasma leakage tendency in patients with DF. The third important component of the plasma leakage triad is the findings of gallbladder wall thickening in patients with DF. Enlargement of liver (Hepatomegaly), enlargement of spleen (splenomegaly) and less regularly, increase in the volume of pancreas have been described.

Patients	Age (years)	Incidence of pleural effusion	Incidence of ascites	Incidence of gallbladder wall thickening
169	27.9±13.4	48(28.4%) right sided 19(11.2%)bilateral	126(74.6%)	122(72%)[38]
56	2-9	Day 5-7: 66 % left sided 87.5 % right sided	Day 5-7: 96%	Day 5-7: 100% [39]
240	28.9 ± 12.4	Right sided 82 (74.5 %)	68(47.2%)	51(23.7%)[40]
12	Clinical trial on subjects	54 %	54%	54%[41]
85	20-50	37% right sided,22% bilateral	36%	45% [42]
170	Not reported	57 % (97)	56 % (96)	Notreported [43]
83	34.6 ± 14.23	3(3.6%)	3(3.6%)	35(42.2%)[44]
746	1-10	363(47%)	296(40%)	532(72%)[45]
86	31.5-43	21(32%)	24(37%)	38(59%)[46]
40	16-65	21(53%)	6(15%)	17(43%)[47]
158	Pediatric patients	62 %	52 %	43 %[48]
66	Group I: 22,Group II:19	Group I: 2(4%) Group II: 0%	Group I: 6 (11%), Group II: 5 (45%)	GroupI: 37(67%) GroupII:11(100% [49]
37	Pediatric patients	27(70.3%)	29(78.4%)	33(89.2%)[50]
69	24.2± 10	2(2.9%)	10(14.5%)	37(53.6%)[51]
254	7± 3.3	13(5.1%)	18(7%)	25(9.8%)[52]
148	Pediatric patients	Grade II-II: 30%, Grade III-IV: 95%	GradeI-II: 34% Grade III-IV: 95%	Grade II-II: 32% Grade III-IV: 95% [53]
171	12-70 years	72(45.6%)	37(23.41%)	99(62.5%)[54]

Table 1: Comprehensive data of Pleural effusion, Ascites, GB wall thickening

The collection of serous fluid in the pericardial cavity resulting from hyper-permeability of the microvasculature induced by the DF is less frequently observed and the reported incidence in the published literature is extremely variable, up to 28.5 % in patients with DF mainly seen on day 5 to day 7 of the onset of symptoms. The collection of fluid around the gallbladder is also indicative of microvasculature hyperpermeability induced by the consequences of DF.

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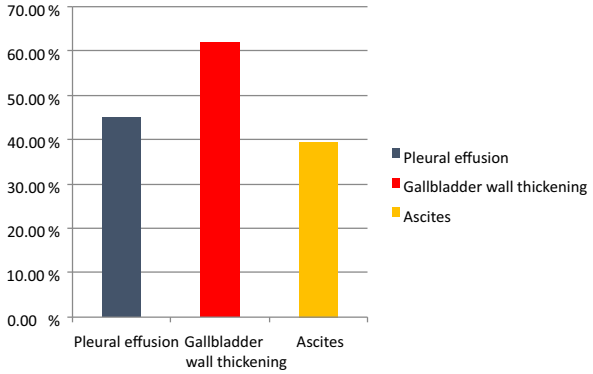

Figure 1: The percentage of incidence of plasma leakage triad

DISCUSSION

Based upon the findings of current systematic review, the ultrasonography is an effective diagnostic modality in the management of DF. The sensitivity of the ultrasonography is significantly higher to diagnose early or late features of plasma leakage resulting from the microvasculature hyper-permeability. In addition, the gallbladder wall edema showing as thickening of GB wall and cavitary effusion (pleural, peritoneal) are observed in conjunction with the nausea, vomiting, severe abdominal pain, and raised levels of hematocrit [21-24]. Pleural effusion, may be an early warning sing on day 2 of the contracting DF before the development of defervescence which is a preceding change in hematocrit levels [21-30]. The mainstays of ultrasonographic findings are based upon the hyper-permeability of the microvasculature (a sign of plasma leakage) which includes the collection of leaked serous fluid in body cavities such as ascites, pleural effusion and pericardial effusion. The thickening of the gall bladder wall has been reported on almost 33 % patients with DF with milder symptoms. However, the incidence of gallbladder wall thickening has been reported as higher as 95 % in patients developing sign and symptoms of dengue hemorrhagic fever. Furthermore, the presence of ascetic fluid in hepato-renal pouch and peri-renal edema on abdominal ultrasound is also a diagnostic feature in patients with severe DF [21-30]. The incidence of volumetric increase of the spleen, liver and pancreas has also been observed in several reported studies originating as single institution experience but with variable incidence. The abdominal, chest and pelvic ultrasonography was reported the best method for the screening of dengue hemorrhagic fever, with 91.42% sensitivity and negative predictive value of 84.21%. Similarly, the presence of pleural effusion, ascites, hepatomegaly and gallbladder wall thickening were reported quite frequently by several writers as principal ultrasonographic features. Pleural effusion is more commonly observed in severe forms of the DF [28]. Pleural effusion (collection of fluid in pleural cavity) is most regular ultrasonographic feature in patients with plasma leakage. Conventional chest x-ray is associated with the reduced sensitivity compared to the chest ultrasound in the detection of subtle pleural effusion [22-29]. The hyperpermeability of the microvasculature lining the vast space of peritoneal cavity leads to the development of ascites, particularly in patients with severe hemorrhagic dengue fever. The incidence of ascites has been reported with variable rate of 26% to 34% of cases with mild DF. But the increased incidence ranging from 94% to 95% has been reported in patients with severe DF or dengue hemorrhagic fever [32]. Hepatic subcapsular fluid increasing the volume of the liver and hepatomegaly is highly suggestive of severity of the disease but it lack strong evidence. The presence of fluid in the hepato-renal pouch was difficult to locate in mild forms of DF but as higher incidence as 71 % has been reported in patients with dengue hemorrhagic fever, thus indicating a significant marker for disease severity [25]. In the cases of dengue hemorrhagic fever, gallbladder wall thickening of more than 5 mm has shown sensitivity of 93.8%. The specificity achieves 91.7%, when the gallbladder wall thickening is more than 5.0 mm, which may be a marker that tells there's greater possibility for progressing towards shock [32]. A large study published on children afflicted with DF of variable intensity [26] indicated that patients in which dengue test is positive, have shown thickening of GB wall in 100% of the patients. Pleural effusion is second most common finding, followed by GB wall thickening from the fifth febrile day. Based upon the findings of this study [26], the authors determined that, during an epidemic outbreak of the DF or dengue hemorrhagic fever, the GB wall thickening in a patient with fever, should suggest that there is possibility of dengue fever or dengue hemorrhagic fever [37].

CONCLUSION

Third space extravasation of the body fluids is a critical phase of the DF demonstrating in subtle pleural effusion, ascites and gallbladder wall congestion which may not be apparent on the general physical examination undoubtedly would add value in the evaluation of many tropical infectious diseases like DF, allowing clinicians access to early findings that may guide initial diagnosis and management. Ultrasonic features of severe DF include pleural effusion, pericardial effusion, ascites, abdominal visceromegaly, gallbladder wall thickening, and diffuse peripheral edema.

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