Brief Reports

A Reappraisal of the Criteria to Diagnose Plasma Leakage in Dengue Hemorrhagic Fever

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A study was undertaken to analyze the usefulness of radiographic and ultrasonographic findings and area specific hematocrit cut off values in Dengue Hemorrhagic Fever (DHF). Of the 65 cases, 35 were DHF and 30 were Dengue Fever as per the WHO case definition. Among the DHF cases, hemoconcentration (>20%) was detected in 20 cases (57.14%), hypoproteinemia in 11 (31.42%) and clinical evidence of pleural effusion and or ascites in 25 (71.42%). Hemoconcentration based on area specific hematocrit cut off values was observed in 32 cases (91.42%). Ultrasonographic evidence of plasma leakage was seen in 32 cases (91.42%). In detecting plasma leakage, area specific hematocrit cut off values and ultrasonography had the highest sensitivity (91.42%), while ultrasonography had the highest negative predictive value of 84.21%. Clinical evidence of plasma leakage was more frequent than hemoconcentration or hypoproteinuria. Ultrasonography is an ideal non-invasive investigation to detect plasma leakage and area specific hematocrit values are useful as evidence of plasma leakage.

Key words: *Dengue, Hemorrhagic fever, Plasma leakage.*

THE WHO guidelines(1) for detection of plasma leakage for diagnosis of Dengue Hemorrhagic Fever (DHF) by various indirect evidences have revolutionized the concept of managing cases of DHF. The need to have area specific hematocrit cut off values to identify hemoconcentration as evidence of plasma leakage has been suggested(2) and studies from Delhi and Chennai have recommended such values(3,4). There has been paucity of data regarding the usefulness of ultrasonography and radiography in the diagnosis of DHF. Hence this study was carried out to study the radiological and ultrasonographic features in DHF and their role in the detection of plasma leakage. This study also compared the various parameters indicating plasma leakage including area specific hematocrit values with the radiological and ultrasonographic evidence of the same.

Subjects and Methods

A prospective study was undertaken at Kanchi Kamakoti CHILDS Trust Hospital, a tertiary care referral Pediatric hospital, in Chennai from December 2003 to May 2004. All children (>1 month upto 18 years of age) who were diagnosed to have dengue infection

and hospitalized for the same were included in the study. Apart from a meticulous clinical examination carried out daily, all the children underwent the following investigations as per the requirement of the study–complete blood count, liver function tests, renal function tests, chest *X*-ray and ultrasonography. Repeat hematocrit and platelet count were done at recovery or as and when required depending on the clinical situation. All children were confirmed to have diagnosis of dengue virus infection by doing the dengue ELISA IgG and IgM test (Pathozyme dengue IgG and Pathozyme dengue IgM, Omega Diagnostics Ltd., Alloa, Scotland, UK) on their serum samples. All clinical and investigation parameters were recorded in a well-structured format from the time of admission to the time of discharge. Clinically, presence of tachypnea, chest retractions, decreased breath sounds and decreased vocal resonance were considered signs of pleural effusion. Presence of abdominal distension with fullness of the flanks and presence of shifting dullness/fluid thrill was taken as evidence of ascites. The extent of hemoconcentration in our study was quantitated by taking a difference between the maximum hematocrit at admission or anytime during the hospital stay and the minimum hematocrit recording at convalescence or discharge. For the purpose of the study DHF was diagnosed as per the WHO guidelines(1) as a probable case of dengue fever with hemorrhagic tendencies and thrombocytopenia along with the presence of evidence of plasma leakage manifested by any one or more of the following *i.e.,* a rise in the average hematocrit for the age and sex by >20%; a >20% drop in the hematocrit following volume replacement compared to the baseline; signs of plasma leakage *i.e.,* pleural effusion, ascites, hypoproteinemia.

Children who were found to be sero-negative for dengue infection, children with overlap infection with other organisms in addition to dengue infection, children receiving treatment for dengue infection on out patient basis and children who received blood transfusion during the present admission were excluded.

The area specific hematocrit cut off values for hemoconcentration was defined by the study done in Chennai as >34.8% in less than 5 years age group and >37.5% in the age group of more than 5 years(4). Our study also attempted to test the utility of this hematocrit cut off value in recognizing hemoconcentration.

The radiological and ultrasonographic evidence of plasma leakage was compared with the other parameters of plasma leakage.

Percentage analysis was carried out on the data of various evidences of plasma leakage as well as area specific hematocrit cut off values. Sensitivity, specificity, positive predictive value and negative predictive values were derived from the available data pertaining to the imaging modalities and were compared with the other parameters of plasma leakage.

Results

In the present study of a total number of 65 cases, 30 cases (46.15%) were Dengue fever (DF) and the remaining 35 cases (53.84%) were Dengue Hemorrhagic Fever (DHF) based on the WHO case definition. Only 6 (9.23%) of the 65 cases had Dengue Shock Syndrome (DSS).

The various USG findings in cases of Dengue virus infection in our study are depicted in *Table I* and the comparison of the parameters giving evidence of plasma leakage in children with DHF depicted in *Table II.*

The comparison of various parameters that give evidence of plasma leakage is as follows.

TABLE I–*Ultrasonographic Findings in DF* and DHF*.*

Ultrasonographic findings	Total (n = 65)	DF (n = 30)	DHF (n = 35)
Ascites	46(70.76%)	14(46.66%)	32(91.42%)
Pleural fluid	44(67.69%)	13(43.33%)	31(88.57%)
Gallbladder Changes	42(64.61%)	10(33.33%)	32(91.42%)
Hepatomegaly	56(86.1%)	22(73.33%)	34(97.14%)
Splenomegaly	18(27.6%)	7(23.33%)	11(31.42%)
Perinephric fluid	10(15.3%)	0	10(28.57%)

*DF and DHF based on the WHO case definition.

TABLE II–*Evidence for Plasma Leakage in Children with DHF*.*

Evidence for plasma leakage	DHF(n = 35)
Hemoconcentration >20%	20(57.14%)
Hypoproteinemia	11(31.42%)
Clinical evidence of plasma leakage(pleural effusion and or ascites)	25(71.42%)
Hemoconcentration as per Area specific hematocrit cut off levels	32(91.42%)
Evidence of plasma leakage on Radiography(pleural effusion)	23(65.71%)
Evidence of plasma leakage on USG(pleural effusion and or ascites)	32(91.42%)

*DHF as per the WHO case definition

Hemoconcentration (>20%) was detected in 20 (57.14%) out of the 35 cases of DHF. Hemoconcentration based on the area specific hematocrit cut off values was observed in 32 cases (91.42%) and it had a better sensitivity and negative predictive value as an indicator of plasma leakage. (*Table IV*)

Hypoproteinemia was seen only in 11 cases (31.42%) of DHF in our study. Most of the cases of DHF (24 cases, 68.57%) did not have hypoproteinemia. Hypoproteinemia had a sensitivity of 25% and negative predictive value of 46.87% as evidence for plasma leakage (*Table III*).

Clinical evidence of plasma leakage in the form of pleural effusion and or ascites was present in 25 out of 35 cases (71.42%) of DHF. However, in comparison to the laboratory parameters of plasma leakage (hypoproteinemia and hemoconcentration), clinical evidence of plasma leakage (signs of pleural effusion and or ascites) was observed more frequently. This parameter had a sensitivity of 56% and negative predictive value of 72.50%.

Radiographic evidence of pleural effusion was present in 23 (65.71%) out of the 35 cases of DHF. Among those who had radiographic evidence of pleural effusion only 9 cases (39.13%) had clinical evidence of the same. Out of 30 cases labelled as DF as per the WHO recommended case definition, 6 cases (20%) had pleural effusion on radiography. These 6 cases did not have 20% hemoconcentration, clinical evidence of plasma leakage or hypoproteinemia to be labelled as DHF. Chest radiography had a sensitivity of 65.71%, specificity of 80%, positive predictive value of 79.31% and negative predictive value of

TABLE III–*Comparative Analysis of Parameters for Evidence of Plasma Leakage.*

	Clinical Evidence	Hemoconcentration >20%	Hypoproteinemia	Ultrasound	*X*-ray
Sensitivity	56.00%	48.27%	25.00%	91.42%	65.71%
Specificity	72.50%	83.33%	90.90%	53.33%	80.00%
Positive predictive value	56.00%	70.00%	72.72%	69.56%	79.31%
Negative predictive value	72.50%	66.66%	46.87%	84.21%	66.66%

TABLE IV–*Comparison between WHO Criteria for Hemoconcentration and Area Specific Hematocrit Cut off Values as Evidence of Plasma Leakage.*

	Hematocrit >20%	Area specific hematocrit cut off values
Sensitivity	48.27%	91.42%
Specificity	83.33%	46.66%
Positive predictive value	70.00%	66.66%
Negative predictive value	66.66%	82.35%

66.66% in identifying plasma leakage.

Out of the 35 cases of DHF, pleural effusion was detected by ultrasonography in 31 cases (88.57%). Among them only 11 cases (35.48%) had pleural effusion on clinical examination and 23 cases (74.19%) had radiographic evidence of the same. 20 cases (64.51%) did not have any clinical evidence of pleural effusion and 8 cases (25.80%) did not have radiographic evidence of the same. With the assistance of ultrasonography, 13 cases labelled as DF as per the WHO criteria (43.33%) were found to have pleural effusion and therefore would qualify to be labelled DHF. There was no case in our study group that had pleural effusion in chest radiography that was not evident in ultrasonography.

Out of the 35 DHF cases ascites on ultrasonography was present in 32 cases (91.42%) while clinical evidence of the same was seen in only 20 cases (57.14%). When ultrasonography was included as a tool in the detection of ascites 14 out of the 30 cases (46.66%) labelled as DF as per the WHO parameters were found to have ascites and therefore would qualify to be labelled as DHF instead. Ultrasonography had the highest sensitivity (91.42%) and negative predictive value (84.21%) when compared with all the other parameters in detecting plasma leakage (*Table III*).

Discussion

There are difficulties in following the WHO criteria for recognizing plasma leakage, for diagnosis of DHF(1), since hemo-concentration (>20%) is usually diagnosed retrospectively, hypoproteinemia is infrequent and clinical recognition of plasma leakage is difficult in a sick child. Ultrasonography and radiography of the chest can reliably detect presence of pleural effusion and ascites in children with DHF.

In our study, ultrasonography was found to be superior when compared with radiography in detecting plasma leakage. The low

Key Messages

- Repeated clinical assessment helps recognize plasma leakage in DHF.
- Ultrasonography is superior to clinical and laboratory parameters for diagnosing plasma leakage.
- Area specific hematocrit cutoff values are useful in the diagnosis of DHF.

sensitivity of radiography could be attributed to the following reasons.

Radiographic films are not ideal for detecting small amounts of effusion, while sonography is highly useful(5-9). Lateral decubitus chest radiography and chest sonography have been proven to be highly efficient methods compared to conventional radiography to detect small amounts of pleural effusions(5-9). In our study, lateral decubitus films were not carried out. Also, the practical difficulty in getting these two investigations done at the same time could have contributed to these results. An earlier study from Indonesia also reported such discrepancies in the findings related to the two investigations(10). The chest radiographs in our study were carried out at the time of admission or at the time when there was a dilemma in diagnosing DHF. A repeat chest radiograph at an appropriate time, which could have resulted in a higher yield, was not carried out on our children for the concern of radiation exposure. Six cases that were defined as DF as per the WHO case definition did not have hemoconcentration, hypoproteinemia or clinical signs of pleural effusion but had radiographic evidence of pleural effusion confirming plasma leakage. Thus radiography was better in comparison to the WHO recommended parameters in detecting plasma leakage.

Out of the 65 cases screened by ultrasonography, evidence of plasma leakage in the form of pleural effusion and or ascites was seen in 46 cases (70.76%) and, therefore, would qualify to be DHF. However we had only 35 cases of DHF based on the WHO parameters, *i.e.*, not using USG to detect pleural effusion or ascites. Therefore when USG was also used apart from the clinical and the biochemical criteria to screen these cases the total no of cases of DHF would be 49 and DF cases would be 16. The reason for this discrepancy could be that at the time ultrasonography was done, the amount of capillary leak was probably minimal to be detected clinically. The sensitivity of detecting ascitic fluid might have improved by clinical methods other than shifting dullness like elicitation of puddle's sign, which was not carried out in the present study since it was not feasible practically in these sick children. When the various parameters suggested by WHO as indirect evidences of capillary leak were compared with ultrasonography and radiography, ultrasonography was found to have the highest sensitivity and negative predictive value in detecting plasma leakage (*Table III*). Ultrasonography would be ideal owing to its safety in that it is non-ionizing and would assist detecting plasma leakage even before it clinically manifests. Similar findings have been reported earlier from Indonesia(11).

Hemoconcentration of more than 20% was found to have a lower sensitivity and negative predictive value compared to hemoconcentration based on the area specific

hematocrit cut off levels (*Table IV*), thus supporting the use of area specific hematocrit cut off values as recommended in earlier studies(2-4).

Clinical evidence of pleural effusion and or ascites was present more often among cases of DHF than hemoconcentration (>20%) and hypoproteinemia. This could be attributed to the fact that clinical examination of our cases was being carried out more often and periodically while blood investigations were not so frequently done. This highlights the importance of a meticulous clinical examination repeatedly in children with dengue virus infection in the recognition of plasma leakage early.

The low sensitivity and low negative predictive value of hypoproteinemia indicated that this tool was not sufficiently sensitive to pick up plasma leakage early.

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