ORIGINAL ARTICLE

Identification of factors predicting mortality in Dengue infection associated liver failure

Varma Sharat, Consul Megha, Kukreja Shyam, Saikia Bhaskar, Uttam Rajiv, Das Dibyajyoti, Bhatia Naveen, Gupta Subhash
Emails and Affiliations :
varma.sharat@yahoo.com - Sharat Varma - Paediatric Gastroenterology and Hepatology - Max Saket ,New Delhi
bhaskar_67@rediffmail.com - Bhaskar Saikia - Dept of Paediatrics, Max Saket,New Delhi
rajivuttam@hotmail.com - Rajiv Uttam - Dept of Paediatrics , Max Patparganj,New Delhi
drshyamkukreja@gmail.com - Shyam Kukreja - Dept of Paediatrics, Max Patparganj ,New Delhi
dibya_das79us@yahoo.com - Dibyajyoti - Centre for liver and biliary sciences, Max Saket ,New Delhi
rajnavinb@gmail.com -Naveen Bhatia – Department of Paediatrics ,Max Gurgaon ,Haryana
livertransplant@gmail.com - Subhash Gupta - Centre for liver and biliary sciences,Max Saket ,New Delhi
Corresponding Author : *Dr. Megha Consul ,Max Hospital Gurgaon*
Email : meghaconsul@gmail.com
Address for Correspondence : Dr Megha Consul ,Principal Consultant,Max Hospital Gurgaon ,Haryana ,ph : +919818227924
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Abstract

Objectives: To identify factors predicting mortality in acute liver failure due to Dengue infection

Methods: Retrospective analysis was done to identify factors predicting mortality among children having acute liver failure (ALF) due to Dengue infection. Children admitted in Max Hospital PICU's between May 2017 and May 2019 ALF was diagnosed by PALF criteria ;Dengue infection was diagnosed if NS-1 Antigen and/or IgM Dengue antibody were positive. Other causes of ALF were ruled out and all received standard of care treatment for ALF. The highest value of ammonia, urea, creatinine, AST, ALT, bilirubin, PT and apTT during the illness and lowest value of haemoglobin, leucocyte count, platelet, albumin, during the course of the illness were recorded. For continuous variables, mean was calculated and student T test was used to compare . Binary logistic regression was used and AUROC was calculated to determine cut off values and compare the utility of various parameters for the same.

Results: 15 children (8 boys) with mean age of 106 months were included. 8 of 15 had poor outcome (53% mortality). There was significant difference in ammonia, AST, ALT, aPTT levels between the survivors and non-survivors. Cut off values predicting mortality with sensitivity of 88% and specificity of 86% were increase of AST, ALT aPTT by 1750,1011 IU/L and 53 seconds respectively; on a daily basis. Kings college criteria in poor outcome had sensitivity of 100% but poor specificity of 55.6%.

Conclusion : Rate of increase of AST, ALT, aPTT with appropriate cut off values can predict the outcome of Dengue induced ALF better than Kings College criteria.

KEYWORDS: dengue infection, dengue hemorrhagic fever, atypical manifestations of dengue fever, hepatic failure in dengue

Disclosures / Conflicts of interest: None

Introduction: Dengue is the most common arboviral disease and second most common mosquito borne disease globally. 100 countries are endemic for this illness and these are mostly developing or under-developed nations. (1,2) The disease effects multiple organs, of which liver is the most commonly affected. The manifestations can range from asymptomatically elevated transaminase levels to liver failure (3-10). There have been reports on the use of NAC, MARS, plasmapheresis and also one case of liver transplantation in liver failure management in Dengue infection (11,12,13). There exist many lacunae in our understanding of paediatric dengue liver failure which are contributory to the associated high mortality. There are no risk stratification markers and the applicability of Kings Collge criteria that is frequently used, has not been validated in this indication. Appropriate high risk factor identification would help in selecting the patients to receive more intensive care, before the point of irreversibility. With this background, we designed this study to identify easily applicable clinical parameters that would allow to identify the Dengue patients at highest risk.

Patients: Children of age less than 16 years having clinical features consistent with Dengue and having either NS1 antigen or Dengue IgM positive, meeting the criteria for ALF (INR > 2) and admitted in PICU

presentation and hence found in higher propensity among the cohort of children who did not survive. We did not do IVC diameter assessment as a standard practice and that perhaps could have provided a definitive answer to this hypothesis.

The peak AST level and rate of change of AST both have higher significance than the ALT in our study. This is in concordance to earlier studies which have indicated that AST is more correlated to the infection via a mitochondrial involvement pathway (3,14,15,16). Similarly the aPTT we observed was of more value than the PT, which is also in line with the previous evidence. (4,6,17, 18)

The dynamic characteristics of rate of change of AST, ALT, aPTT on a daily basis give us tools which have a direct clinical applicability, in identifying children who would have worse outcome and hence receive more aggressive care. An increase of AST, ALT aPTT by 1750,1011 IU/L and 53 seconds respectively; on a daily basis identify children with poor outcome with sensitivity of 88% and specificity of 86%. Considering the high rate of mortality in ALF due to Dengue illness (40%) and the geographic predisposition of the infection in developing countries, we need to identify early predictors that are easily available and cost-effective(14,18,19,20). The earlier identification of such children would allow for lower threshold of intensive treatment modalities which have shown some benefit like plasmapheresis, MARS, liver transplantation; in this subgroup of patients. (11,12,13)

The Kings College criteria was also applied in this cohort and we found the negative predictive value to be helpful (100%). A negative test, when interpreted carefully could be as helpful. These criteria have been validated in infectious hepatitis but in Dengue ALF we can observe the limitations as the specificity was only 55.56%.

Our study has limited number of children (n=16) but yet is one of the larger studies on ALF related to Dengue. This highlights the need for more multi-centric and collaborative work to improve the outcomes of this common infection. (20)
In conclusion, Dengue ALF has high mortality and the dynamic change in AST, ALT and aPTT are good clinical indicators of the children at high risk for poor outcome.

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between May 2017 and May 2019 were included. Hepatic encephalopathy is difficult to assess in a child with Dengue illness, hence the criteria of INR >1.5 with encephalopathy was not used in diagnosing ALF. Those having a co-infection were excluded, namely - Hepatitis A, Hepatitis B, Hepatatis C, Salmonella, Leptospira. Also excluded were children with evidence of underlying chronic liver disease or those with inadequate data retrieval. The updated WHO guidelines for treatment of dengue in children were used to base our management protocols.

Methods: This was a retrospective, multi centric study wherein the clinical, biochemical data was retrieved from the EMR system of the hospital. The participating centres are part of the common group, are all linked via a central EMR system, central referral laboratory and follow common protocols. The centres were Max hospital in Delhi-NCR; Gurgaon, Patpatganj and Saket.

For the children who satisfied the inclusion - exclusion criteria, data was collected on a pre-decided format. In addition to the demographic data, biochemical parameters were evaluated at admission and at peak or lowest levels, as applicable. The rate of change of a parameter was calculated as the difference between parameter at admission and then at the peak or lowest value, divided by the number of days between the two readings.

The parameters selected for inclusion in the study were duration of ICU stay, hemogram, LFT, PT-aPTT, Urea, Creatinine and ammonia levels.

Statistics: Continuous variables are presented as mean values and standard deviation (SD). Continuous variables were compared using independent t test. To compare the data between survivors and non-survivor groups, binary logistic regression was used. AUROC was calculated to determine cut off values and compare the utility of various parameters for the same. P value was considered to be significant when it was below 0.05. The SPSSTM (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) was used for statistical analyses.

Results: The cohort description, inclusion characteristics and outcomes are given in table 1. 16 children were included in the study and we observed a mortality rate of 44% (7 of 16).

Comparison of admission characteristics between those who died and survived are outlined in table 2. We observed significant differences in the ammonia, PT, aPTT durations, haemoglobin levels and duration of ICU stay.

Comparison of peak/lowest characteristics between those who died and survived are outlined in table 3. There was significant difference in ammonia, PT and aPTT durations as before but peak AST and ALT levels were also significant. The previous characteristics of haemoglobin, TLC were no more significant.

Comparison of rate of change of characteristics between those who died and survived were calculated for all parameters and were of significance only for aPTT duration, AST and ALT. These are outlined in table 3.

Kings college criteria for LT were met in all 7 who died and also in 4 of 9 who survived. Hence the sensitivity was 100% but specificity was 55.6%. The positive and negative predictive value were 63.6% and 100% respectively.

AUROC analyses for cut off identification were done and highest AUROC was seen for peak AST, rate of change of AST and ALT. The optimal cut off values selected with their sensitivity and specificity are detailed in table 4.

Discussion: This is the first study on pediatric dengue ALF to identify biochemical characteristics at admission and their dynamic evolution to predict final outcome. We also studied the limitations of Kings college criteria in this scenario.

We observed that Hb, TLC, Creatinine and ammonia at admission were significantly higher in the children who died in comparison to the survivors. In subsequent analysis i.e with the peak values or when evaluating the rate of change, these parameters were not significant. We would be sceptical to use admission lab parameters as the duration of illness would have been different before reporting to the hospital, hence we trust the dynamic, evolution pattern of a laboratory parameter more. More so it would give us an index to monitor the progress on a daily scale rather than a fixed scale at the beginning. Dengue infection causes fluid leakage of fluid from the intra-vascular space, hence the Hb, TLC, Creatinine and ammonia elevations may suggest a haemoconcentration effect or inadequate fluid intake. Accordingly, children with higher haemoconcentration would have more severe

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