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Research Article

STUDY OF CLINICAL AND LABORATORY PREDICTIVE MARKERS FOR ACUTE DENGUE FEVER IN CHILDREN

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ABSTRACT
Early diagnosis of dengue virus infection during the febrile stage helps for adjusting appropriate management. This study was done to identify the clinical and laboratory predictive markers in the acute stage of dengue infection as well as to identify the statistical significance of clinical markers & laboratory parameters in early stage of Dengue fever in children. A prospective, hospital-based study was conducted over a period of two years from November 2014 to October 2016 on Dengue cases of Pediatric age group (1- 18 years). Children with fever of less than 7 days duration, with clinical features suggestive of Dengue fever as described in WHO 2012 Guidelines, were enrolled. A pre-structured proforma was used to record the clinical data and laboratory parameters from individual case selected for the study. The patients were managed according to WHO 2012 protocol. Total 280 cases of Dengue fever (as per WHO 2012 Guidelines) were studied out of which 71% cases had positive Dengue serology. Among the 200 cases with positive Dengue serology, in addition to fever (which was an inclusion criteria) the other clinical predictors were myalgia, nausea/vomiting, anorexia and flushing. The sensitivities of myalgia, nausea/vomiting and flushing were 56%, 53%, and 41%, while the specificities for above features were 60%, 75% and 80%, respectively. The combination of nausea/vomiting, flushing, myalgia and pain abdomen showed a PPV of 82.8% and a NPV of 35%. The hematological and biochemical predictive markers were leukopenia, thrombocytopenia, prolonged aPTT and elevated AST. The sensitivities of thrombocytopenia, leucopenia and elevated AST are 72%, 71%, and 71%, while the specificities for above features are 86.2%, 62.5% and 57.2%, respectively. In positive Dengue serology cases, Positive Predictive Value for the combination of leukopenia, thrombocytopenia, prolonged aPTT and elevated AST was found to be 85.3%, while the Negative predictive value is 48.6%. These combinations of clinical and laboratory predictive markers will help in early diagnosis of dengue infection. Dengue fever presents like any other viral fever, however certain clinical signs like, anorexia, nausea/vomiting, myalgia and flushing are symptoms commonly associated with this. Lab parameters of leukopenia, thrombocytopenia and altered coagulation parameters with elevated liver enzymes also have a positive correlation. Use of these parameters may serve as surrogate markers of Dengue infection if confirmatory tests are not available.

Keywords: *Dengue, Early Diagnosis, Predictive Markers*

INTRODUCTION
Need for Study
Dengue is the most prevalent mosquito-borne viral disease in humans, occurring in tropical and subtropical countries of the world where over 2.5 billion people are at risk of infection.
The frequency of Dengue and its complications has increased over the past few years, especially in rural Bangalore.
Dengue has a wide spectrum of clinical presentation, unpredictable clinical evolution and outcome, especially in children.
Early prediction of Dengue infection during any febrile illness, using clinical and laboratory markers, is essential for initiating early appropriate management (Ramos *et al.*, 2009). This study is aimed to identify the statistical significance of these clinical and laboratory predictive markers in early stage of Dengue fever in children of rural Bangalore.

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Review of Literature

Kalayanarooj (1997) in a prospective observational study conducted to identify early indicators of acute dengue virus infection in 172 evaluable subjects, found that children with dengue were more likely than children with other febrile illnesses (OFI) to report anorexia, nausea, and vomiting and to have a positive tourniquet test, and they had lower total white blood cell counts, absolute neutrophil and absolute monocyte counts, and higher plasma alanine and aspartate (AST) aminotransferase levels than children with OFI.

Plasma AST levels were higher in children who developed DHF than in those with DF. These data identify simple clinical and laboratory parameters that help to identify children with DF or DHF.

Ho *et al.,* (2013) in a hospital based prospective study among the 581 suspected dengue cases patients to identify clinical and laboratory predictive markers for acute dengue infection, consisting of 100 children (<18 years) and 481 adults found that the most common symptoms/signs at admission were myalgia (46.8%), petechiae (36.9%) and nausea/vomiting (33.5%).

The most notable laboratory findings included leukopenia (2966 ± 1896/cmm), thrombocytopenia (102 ± 45 × 103/cmm), prolonged activated partial thromboplastin time (aPTT) (45 ± 10 s), and elevated serum levels of aminotransferase (AST, 166 ± 208 U/L; ALT, 82 ± 103 U/L) and low C – reactive protein (CRP) (6 ± 11 mg/L).

Based on the clinical features for predicting laboratory-confirmed dengue infection, the sensitivities of typical rash, myalgia, and positive tourniquet test are 59.2%, 46.8%, and 34.2%, while the specificities for above features are 75.4%, 53.5% and 100%, respectively. The positive predictive value (PPV) for combination of leukopenia, thrombocytopenia (< 150 × 103/cmm), elevated aminotransferase (AST/ALT > 1.5) and low CRP (< 20 mg/L) is 89.5%, while the negative predictive value is 37.4%. Furthermore, the PPV of the combination was increased to 93.1% by adding prolonged aPTT (>38 secs) and concluded that leukopenia, thrombocytopenia, elevated aminotransferases, low CRP and prolonged aPTT, were useful predictive markers for early diagnosis of dengue infection.

Shah and Katira (2005) in a prospective study of 69 suspected cases of dengue with 34 dengue IgM positive cases aged 6months-11years found that the most common clinical manifestation was fever seen in all 34 (100%) patients. The mean duration of fever was 6.38 days with the median of 4 days, 19 patients (55.9%) had hypotension, 17 patients (50%) had vomiting. Hepatomegaly was seen in 16 patients (47.1%) and bleeding tendencies in the form of melaena and haematemesis were seen in 13 patients (38.2%). Six patients (17.6%) also had splenomegaly. Five patients each (14.7%) had erythematous rash and congestive cardiac failure (CCF). Two patients (5.9%) had bradycardia.

Rathakrishnan *et al.*, (2014) in a longitudinal descriptive study conducted among 504 patients aged 14 years and above found that the clinical symptoms of the dengue suspected patients in general included vomiting (59.1%), myalgia (56.3%), arthralgia (49.8%), diarrhea (45.4%), various cerebral symptoms including headaches, and retro-orbital pain (30.0%) nausea (28.4%), rashes (10.3%) and petechiae (0.8%). The warning signs in patients included a concurrent increase in hematocrit with the decrease of platelets, abdominal pain and tenderness (52.0%), bleeding tendencies (17.1%), postural giddiness (24.4%), hepatomegaly and tenderness (22.6%), splenomegaly (0.8%), pleural effusion (1.4%) and ascites (0.4%). An overwhelming 42.9% of recruited patients were also diagnosed with acute hepatitis.

Objectives of Study

A) To study the clinical predictive markers in suspected Dengue fever in children.

B) To study laboratory predictive parameters in suspected Dengue fever in children.

C) To identify the statistical significance of clinical markers & laboratory parameters in early stage of suspected Dengue fever in children.

MATERIALS AND METHODS

Study Design: Hospital based Prospective study

Source of Data: The study will be conducted over a period of two years from November 2014 to October 2016 on suspected dengue cases of Pediatric age group in MVJ Medical College and Research Hospital.

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Study Population

- Children (1- 18 years) with fever of less than 7 days duration, with clinical features suggestive of Dengue fever as described in WHO (2012) Guidelines, will be enrolled.

Clinical Predictors (WHO, 2012 Guidelines)

The following Symptoms/Signs as Clinical predictors will be noted-
lethargy, rashes, myalgia, petechiae,
nausea ± vomiting, arthralgia, hepatomegaly > 2cm,
hypotension, hemorrhage, +ve tourniquet test,
fluid accumulation and abdominal pain

Laboratory Predictors

The following laboratory predictors will be recorded-
Haematocrit, WBC, Platelet, LFT, PT & aPTT and USG abdomen.
DIAGNOSTIC TESTS FOR DENGUE by *(Dengue Day1 Test by J. Mitra & Co.) (Dengue DAY 1 Test, No date).
NS1 Antigen and IgM for Dengue* using rapid solid phase immuno-chromatographic test for:-
1. The qualitative detection of Dengue NS1 antigen and
2. Differential detection of IgM to Dengue virus in human serum/plasma.
Cut off values for laboratory tests:-

- Leucopenia (WBC<5000/cumm),
- Thrombocytopenia (platelet count<1 lakh)
- elevated serum AST OR ALT
- Prolonged PT, aPTT

USG features suggestive of Dengue are:-

- Gall bladder wall edema, Ascites, Pleural effusion and Organomegaly.

Statistical Data Analysis

- Data was entered, charts and tables were generated using Microsoft Excel and Microsoft Word. Qualitative variables were presented as percentages and Quantitative variables presented as Mean ±SD.
- Sensitivity, Specificity, Postive Predictive Value and Negative Predictive Value of the items for predicting Dengue infection was determined for each assigned cut-off value.
- Chi-Square test and Z-test was used to test the difference between serology positive and serology negative dengue cases. 'p' value<0.05 considered statistically significant.

RESULTS AND DISCUSSION

Results

Total 280 cases of Dengue fever (as per WHO 2012 Guidelines) were studied out of which 71% cases had positive Dengue serology. Among the 200 cases with positive Dengue serology, in addition to fever (which was an inclusion criteria) the other clinical predictors were myalgia, nausea/vomiting, anorexia and flushing. The sensitivities of myalgia, nausea/vomiting and flushing were 56%, 53%, and 41%, while the specificities for above features were 60%, 75% and 80%, respectively. The combination of nausea/vomiting, flushing, myalgia and pain abdomen showed a PPV of 82.8% and a NPV of 35%. The hematological and biochemical predictive markers were leukopenia, thrombocytopenia, prolonged aPTT and elevated AST. The sensitivities of thrombocytopenia, leucopenia and elevated AST are 72%, 71%, and 71%, while the specificities for above features are 86.2%, 62.5% and 57.2%, respectively. In positive Dengue serology cases, Positive Predictive Value for the combination of leukopenia, thrombocytopenia, prolonged aPTT and elevated AST was found to be 85.3%, while the Negative predictive value is 48.6%. These combinations of clinical and laboratory predictive markers will help in early diagnosis of dengue infection.

Conclusion

Dengue fever presents like any other viral fever, however certain clinical signs like, anorexia, nausea/vomiting, myalgia and flushing are symptoms commonly associated with this. Lab parameters of

leukopenia, thrombocytopenia and altered coagulation parameters with elevated liver enzymes also have a positive correlation. Use of these parameters may serve as surrogate markers of Dengue infection if confirmatory tests are not available.

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