ResearchArticle

A Prospective Study on Clinical and Laboratory Predictive Markers of Dengue Fever in Children in Tertiary Care Hospital

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Abstract: Background: Dengue fever is the world's fastest-spreading mosquito-borne viral disease, with a 30-fold increase in global incidence over the last five decades. It is a major public health concern throughout the world's tropical and subtropical regions. [1] Dengue is classified into Dengue +/- warning signs and severe dengue, which includes Dengue shock syndrome, Respiratory distress syndrome, Dengue hemorrhagic fever, and organ failure, according to WHO 2012 guidelines. *Material & Methods* : Study Design: Prospective Hospital based observational study. Study area: Department of Paediatrics, Siddhartha Medical College, Vijayawada, Andhra Pradesh. Study Period: 1 year. Study population: All children under the age of 13 years who had acute onset high grade fever and were Non-structural antigen protein 1 [NS1] and/or Immunoglobulin M [IgM] positive were admitted to the paediatric ward. Sample size: study consisted a total of 150 cases. Sampling method: Purposive sampling technique on consecutive cases. The following laboratory test cut-off values are defined: leucopenia (white blood cell count < 4000/mm3), thrombocytopenia (platelet count < 150 103/mm3). Prolonged activated partial thromboplastin time (APTT) (> 38 sec), elevated serum aminotransferase levels (AST or ALT >39 U/L), and low C-reactive protein (CRP) (20 mg/L). The study compared clinical and laboratory parameters in dengue fever, dengue fever with warning signs, and severe dengue. *Result*: Several laboratory parameters were measured as predictors of laboratory- confirmed dengue infections. The positive predictive value of WBC was 80.6%, and NPV of 50% to differentiate the severity of three dengue groups. Whereas, PPV of platelet count was 90.8%, and NPV of platelet count was 50% to differentiate the severity of dengue groups. *Conclusion*: Our research discovered that a combination of commonly used blood tests, such as a white blood cell count, platelet count, liver function tests, and CRP and coagulation profiles, can help detect laboratory-confirmed dengue infection. These clinical and laboratory findings could be used as predictive markers to improve the early detection and severity of dengue infection.

Keywords: Dengue hemorrhagic fever, Predictive markers, CRP levels, PTT.

INTRODUCTION

Dengue fever is the world's fastest-spreading mosquito-borne viral disease, with a 30-fold increase in global incidence over the last five decades. It is a major public health concern throughout the world's tropical and subtropical regions. [1] Dengue is classified into Dengue +/- warning signs and severe dengue, which includes Dengue shock syndrome, Respiratory distress syndrome, Dengue hemorrhagic fever, and organ failure, according to WHO 2012 guidelines. [2]

Laboratory: An increase in HCT is occurring concurrently with a rapid decrease in platelet count. [3] In an endemic area, a child with fever, nausea, vomiting, rash, aches and pain, and a positive tourniquet test is considered to have dengue, which is confirmed by an NSI antigen / IgM antibody study. The following are the lab findings of acute DF: When a fever begins, total WBC is usually normal; however, leucopenia develops with decreasing neutrophils. Initially, platelet counts are normal. Mild thrombocytopenia (100 000 to 150 000 cells/mm3) is common, and approximately half of all DF patients have a platelet count of less than 100 000 cells/mm3, while severe dengue has a platelet count of less than 50000 cells/mm3. [4]

The neutrophil-lymphocyte ratio (neutrophils lymphocytes) and the change in total white cell count (<5000 cells/mm^3) can be used to predict the critical period of plasma leakage. There is a relative lymphocytosis with increased atypical lymphocytes by the end of the febrile phase and into convalescence. A sudden decrease in platelet count to less than 100,000 occurs near the end of the febrile phase, prior to the onset of shock or fever relief. In DF, thrombocytopenia, haemoconcentration, and mildly elevated serum aspartate aminotransferase (AST/SGOT) levels (<200U/L) with an AST: ALT ratio >2 are common findings. [5]

Recovery phase: After the patient survives the critical 24 to 48-hour period, there is a gradual reabsorption of extravascular compartment fluid over the next 48 to 72 hours. Because of the dilutional effect of reabsorbed fluid, the haematocrit stabilizes or may be lower. The white blood cell count usually begins to rise soon after defervescence, but the platelet count usually recovers later than the white blood cell count. [6] Leucopenia, thrombocytopenia, elevated aminotransferases, low CRP, and prolonged APTT are useful predictors of severity of dengue infections. [7]

Hence the present study was undertaken to identify predictive markers of clinical and laboratory findings in dengue infection in children under the age of 13 at a tertiary care Centre.

MATERIAL & METHODS:

This is a Prospective Hospital based observational study was conducted Department of Paediatrics, Siddhartha Medical College, Vijayawada, Andhra Pradesh.

Study population: All children under the age of 13 years who had acute onset high grade fever and were Non-structural antigen protein 1 [NS1] and/or Immunoglobulin M [IgM] positive were admitted to the paediatric ward. Sample size: study consisted a total of 150 cases. Sampling method: Purposive sampling technique on consecutive cases. Inclusion criteria: Children under the age of 13 years admitted to a paediatric ward with acute onset high grade fever and positive Non-structural antigen protein 1 [NS1] and/or Immunoglobulin M [IgM].

Exclusion criteria:
Children with other diseases like enteric fever, rickettsial fever, malaria, leptospirosis, septicemia and other viral hemorrhagic fevers Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study. Study tools and Data collection procedure: Data source: A questionnaire was used for data entry, and all symptoms and lab results were entered and checked by senior consultants.

Method: All children aged below 13 years who presented to the institution's emergency and out-patient departments were included. Cases were chosen based on inclusion and exclusion criteria after parents/guardian's provided informed written consent in their native language and the child provided an asset.

Classification:
After clinical assessment, the patients were classified dengue according to the latest National guidelines for clinical management of Dengue fever, Govt of India. 2015. Dengue is classified as:
1. Mild dengue fever [with no warning signs]
2. Moderate dengue fever
• DF with warning signs
• DF with high risk and comorbid condition
3. Severe Dengue fever

The following laboratory test cut-off values are defined: leucopenia (white blood cell count 4000/mm3), thrombocytopenia (platelet count 150 103/mm3). Prolonged activated partial thromboplastin time (APTT) (> 38 sec), elevated serum aminotransferase levels (AST or ALT >39 U/L), and low C-reactive protein (CRP) (20 mg/L). The study compared clinical and laboratory parameters in dengue fever, dengue fever with warning signs, and severe dengue.

Statistical analysis:
Continuous variables such as demographics and laboratory parameters are displayed as mean standard deviation. Actual numbers and percentages were used to express categorical variables. The one-way ANOVA test was used to compare categorical variables across three groups. For categorical variables, Fisher's exact test was used, and for continuous variables, the t test was used. In all statistical tests, a p value of less than 0.05 was used to indicate a significant difference. SPSS ver 22 (SPSS Inc., Chicago, IL, USA) Windows software was used to compare clinical and laboratory findings. We examined clinical parameters to find the predictive model with the highest sensitivity, specificity, disease prevalence, and diagnosis evaluation accuracy rate. For each assigned cut-off value, the sensitivity and specificity of the items for predicting dengue infection were determined. To compare the useful parameters of test TLC, Platelet, and other laboratory markers, ROC analysis was performed with the best logistic regression results.

RESULT

Table 1. Distribution of study population according to the National Guidelines for Clinical Management of Dengue Fever

Total number of cases	Mild dengue	Moderate dengue	Severe dengue
150 (100%)	80 [53.33%]	41 [27.33%	29 [19.33%]

80 53.3 percent) of the 150 children enrolled in the study group had mild dengue fever with no warning signs, 41 (27.33 percent) had moderate dengue fever with warning signs, and 29 (19.33 percent) had severe dengue fever.

Table 2: Age distribution of the study group

Age (years)	Mild dengue, n=80	Moderate dengue, n=41	Severe Dengue fever, n=29	Total n=150
2-5	30	30	20	80(53.33%)
6-10	21	15	5	41(27.33%)
11-13	8	17	4	29(19.33%)
chi square	2.089			
P value	0.389, Not Significant			

Out of 150 children, there were 80 (53.3%) children in 2-5 years of age, 41 (27.33%) children in 6-10 years group, and 29 (19.33%) children in 11-13 years group respectively. In the present study out of 150 cases studied, 105 (70%) of them were male and 45 (30%) of them were female with male predominance.

DISCUSSION

For a dengue non-endemic area like Taiwan, early case identification is the key for effective dengue control. However, the revised 2009 symptom-based clinical management guideline from the World Health Organization did not require laboratory-confirmation. [8] The revised classification of dengue cases is considered by many to be too broad. Accurate diagnosis of dengue infection is of great important in non-endemic areas like Taiwan, since the goal of dengue control is not only to eliminate the occurrence of severe cases but also to confirm the possible dengue cases. However, the knowledge and practice of healthcare professionals in Taiwan seemed inadequate for the prompt case finding. [9] Universal laboratory for dengue infection are neither economic nor efficient for most countries. Therefore, there is a clinical need to determine who should take the diagnostic test, virological or serological, in daily clinical practice in India.

The early symptom/signs set of acute dengue virus infection is variable and it is difficult to distinguish it from other kinds of febrile illnesses. [10] Our study found that a combination of commonly routine blood tests including white blood count, platelet count, liver function tests, and CRP and coagulation profiles is useful in detecting laboratory-confirmed dengue infection. Previous study in Thailand showed that children with dengue were more likely to report anorexia, nausea, and vomiting and to have a positive tourniquet test. A recent report also showed that patients with bleeding, decrease in total protein, increase in blood urea and decrease in lymphocyte proportion had higher odds for developing dengue hemorrhagic fever. [11]

Simple clinical and laboratory markers can serve as an adjuvant in addition to history and physical examination, and also reduce the possible cost for universal laboratory diagnostic screening. [12] The symptoms combination identified here while having high positive predictive value still had low sensitivity. Therefore it may be a useful addition to the clinical evaluation and there is still a need to identify tests with better sensitivity and specificity. Besides, the accuracy of dengue diagnostic tests depends on the prevalence of dengue and time of sampling. [13]

The difference in clinical manifestation between adult and pediatric dengue infections have been an important issue. A previous study in Taiwan showed that adult patients have higher incidences of arthralgia, myalgia, headache, abdominal pain and upper gastrointestinal bleeding. The adult dengue patient also had lower platelet counts, prothrombin time and serum albumin levels. The incidence of elevated alanine aminotransferase levels and prevalence of dengue hemorrhagic fever in adults are also higher than children. [14] The clinical manifestations in current study showed similarity between adult and pediatric patients during the outbreak. Whereas, the laboratory characteristics demonstrated significant differences of WBC ($p = 0.006$), CRP ($p = 0.011$) and aPTT ($p = 0.021$) between adult and pediatric dengue patients.

CONCLUSION

The overall disease severity in this outbreak is relatively lower than other studies. One of the possible explanations is that most of our patients were infected by dengue virus serotype 1. Dengue virus serotype 2 has been associated with risk factors of developing dengue hemorrhagic fever/dengue shock syndrome. [14] Besides, high accessibility to medical services and low admission threshold provide early intervention and prevent further morbidity/mortality. This practice is in line with the 2009 WHO clinical management guideline, which also encourage admitting patients with danger signs to the medical facilities. [15]

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