



FACTORS PREDICTING SEVERITY OF ILLNESS IN DENGUE FEVER: AN OBSERVATIONAL STUDY

Medicine

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ABSTRACT

Introduction: Dengue is a systemic viral infection caused by the virus from genus *Flaviviridae*. Dengue infection has got a wide clinical spectrum that includes both severe and non-severe clinical manifestations. The group progressing from non-severe to severe disease is difficult to define. Early detection and access to proper medical care significantly lower fatality rates and would help to reduce the burden of hospital stay and economy loss.

Objectives: To study the inflammatory markers predicting the severity of dengue infection.

Methods: 250 diagnosed patients were evaluated with detailed history, physical examination and blood investigations. Inflammatory markers associated with severity of dengue were studied.

Observations and conclusions- 97 patients (39%) had dengue without warning signs, 62(25%) had dengue with warning signs, 63(25%) had severe dengue and 28(11%) had expanded dengue. Low CRP, ESR, HDL and LDL cholesterol were observed in dengue fever, without any statistical significance. Ferritin levels more than 1000 and triglyceride more than 200 was significantly associated with severity of dengue.

KEYWORDS

INTRODUCTION

Dengue is a systemic viral infection caused by the virus from genus *Flaviviridae*. It is transmitted by *Aedes* mosquitoes; *Aedes aegypti* and *Aedes albopictus*.

The incidence of dengue has grown dramatically around the world in recent decades. The disease is now endemic in more than 100 countries. A total of 683,545 dengue cases and 2,576 deaths were reported in India during 2009–2017. Kerala also had a major dengue outbreak in 2017 with 19994 cases and 37 deaths. Identification of reliable and validated predictors of disease severity and mortality is central to reduction of morbidity and mortality by providing early intervention. Studies related to predictors of dengue severity are largely limited especially in south India. This study attempts to identify inflammatory markers associated with dengue and correlate these factors with disease severity.

The new WHO case classification of dengue includes: 1) dengue without warning signs 2) dengue with warning signs and 3) severe dengue. The term expanded dengue syndrome has been coined by WHO to include unusual manifestations of dengue. While most patients recover following a self-limiting non-severe disease, a small proportion progress to severe disease. The group progressing from non-severe to severe disease is difficult to define.

Aim of the study - To study the inflammatory markers predicting dengue shock syndrome, dengue fever with bleeding manifestations, dengue fever with capillary leak, dengue fever with cardiovascular, neurological, hepatic, renal or other organ damage.

MATERIALS AND METHODS

This was an observational study conducted among inpatients admitted

under the Department of General Medicine, Govt. Medical College Kozhikode. Patients diagnosed as dengue cases with either NS1 Ag or IgM positivity (rapid test or ELISA) were included in the study. The Dengue NS1 Rapid Test is a qualitative, membrane-based immunoassay for the detection of NS1 antigen in human serum. The rapid test membrane is pre-coated with a NS1 specific antibody on the test line region and utilizes a separate control to assure assay flow and performance. The dengue IgM Capture ELISA consists of enzymatically amplified sandwich-type immunoassay.

Patients with history of chronic or acute alcohol intake, patients on oral anticoagulation or other coagulation abnormalities, recent intake of any hepatotoxic drugs and patients with NS1 Ag or IgM negative dengue like illness were excluded from the study. A total of 250 patients were studied.

Data was collected by direct interview and clinical examination. Patients satisfying criteria for dengue fever with either NS1 antigen or IgM positive were further evaluated with detailed history and physical examination. Subjects were classified into 4 groups: dengue fever without warning signs, dengue with warning signs, severe dengue and expanded dengue based on WHO case classification. Inflammatory markers studied included ESR, CRP, ferritin, total cholesterol, HDL, LDL and triglyceride.

Data was entered in excel and all analysis were performed with SPSS software. Qualitative variables were analyzed using chi-square test and quantitative variables were analyzed using ANOVA test. Institutional Ethics Committee clearance was obtained.

Criteria for severe dengue:-A case of severe dengue is defined as evidence of severe plasma leakage that leads to shock and/or fluid

accumulation with respiratory distress or severe bleeding or severe organ impairment. Expanded dengue included neurological, hepatic, renal and other isolated organ involvement.

RESULTS

Classification and demography- Total 250 subjects were included in the study. Of the 250 subjects 97(39%) had dengue without warning signs, 62(25%) had dengue with warning signs, 63(25%) had severe dengue and 28(11%) had expanded dengue. In the Expanded dengue, there were 12 cases of hepatitis, 7 cases of pancreatitis, 5 cases of myocarditis, 3 cases of cholecystitis, 2 cases of acute kidney injury and 1 case each of appendicitis, cholecystitis and cerebral infarct. 139 were males and 111 were females. Male to female ratio is 1.25. There is no significant association between sex and severity of dengue. Maximum subjects were in the age group 40-60 followed by 20-40.

Minimum age in the study population was 13 and maximum age 85. Mean age of the study population is 43.94 ± 15.36. Severe dengue was maximum in the age group 20-40 yrs. There was no significant correlation between age and severity of dengue.

Association between inflammatory markers and dengue

Inflammatory markers studied were CRP, ferritin, total cholesterol, HDL, LDL and triglyceride. Mean value of CRP in the study population was 8.18. 33(13.2%) subjects had CRP more than 12. There was no significant association between CRP and severity of dengue (P value 0.371). Mean total cholesterol, HDL and LDL of the subjects were lower than normal range. There was no significant association between total cholesterol, HDL, LDL with severity of dengue.

Mean value of ferritin in the study population was 2061. Ferritin was significantly associated with severity of dengue with a P value of 0.001. 152 (60.8%) subjects had ferritin value more than 1000 and 110 (44%) subjects had ferritin value more than 1500. Of the severe dengue, 53(84.1%) subjects of total 63 had ferritin more than 1000 and 36 (57.1%) subjects had ferritin more than 1500. Ferritin more than 1000 was significantly associated with severity of dengue.(P value 0.001). A subject with ferritin more than 1000 has 19 times risk of developing severe dengue (OR: 19.18) (CI: 8-44)). Mean value of triglyceride in the study population was 194. 106 (42.4%) subjects had triglyceride more than 200. 34 (54%) subjects of the severe dengue had triglyceride more than 200. Serum triglyceride level was significantly associated with severity of dengue (P value of 0.001). Serum triglyceride more than 200 was associated with severe disease with a P value of 0.009 and odds ratio of 2.38(CI: 1.2 – 4.56)

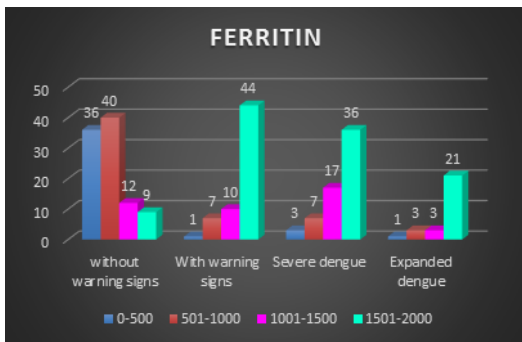
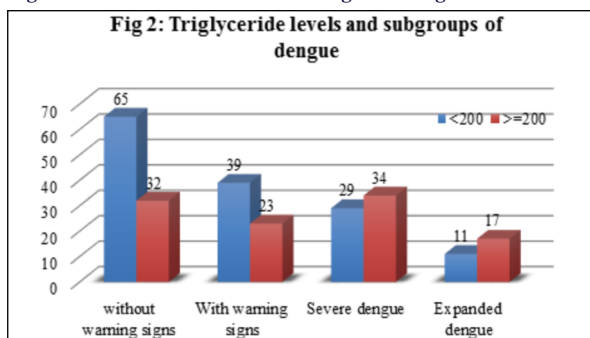


Fig 1: association between ferritin range and dengue



DISCUSSION

Total 250 subjects were included in the study. Subjects with symptoms of dengue as per WHO diagnostic criteria with either NS1 Ag positive

or serologically confirmed IgM positive patients were included in the study.

ESR was not significantly associated with severity (P value: 0.488).Souza et al showed that ESR was within normal ranges in most dengue cases, independent of gender or clinical presentation⁽¹⁾. Kalayanarooj et al showed the mean ESR during the time of shock was lower than in the pre-shock and post-shock period⁽²⁾.

There was no significant association between CRP and severity of dengue (P value 0.371). Few previous studies have shown that CRP levels are elevated in dengue shock syndrome, but other studies have shown that CRP levels in dengue fever is low compared to other febrile illness and help in differentiating dengue from other infections. The study Comparison of the clinical manifestations exhibited by dengue and non-dengue patients among children in a medical centre in southern Taiwan by Pan et al concluded that laboratory findings of leucopenia, thrombocytopenia, elevated levels of liver enzymes, and low C-reactive protein levels were common in dengue patients, and these markers could help confirm the suspicion of pediatric dengue infection⁽³⁾.

Serum ferritin was another inflammatory marker studied. Ferritin more than 1000 was significantly associated with severity of dengue (P value 0.001). In a study by Nadeem et al, out of 31 patients with normal ferritin level only 2 patients developed severe dengue, whereas 35 out of 73 developed severe dengue with ferritin levels more than 1000 and it was concluded that admission day ferritin may serve as biomarker for an early prediction of disease severity in dengue infection⁽⁴⁾. Chaudhuri et al observed that Ferritin may serve as a significant marker for differentiating between dengue fever and fever of other etiology, even in the absence of a positive NS1 antigen or a positive IgM antibody for dengue⁽⁵⁾.

Total cholesterol, HDL and LDL of the subjects were significantly lower than normal range, but there was no association with severity of disease. Biswas et al observed that lower total serum cholesterol and LDL-C levels at presentation were associated with subsequent risk of developing dengue hemorrhagic fever/dengue shock syndrome⁽⁶⁾.

Serum triglyceride more than 200 was associated with severe disease with a P value of 0.009. (OR 2.38 with CI: 1.2 – 4.56). Previous studies have also observed similar findings. Marin- Palma et al observed that triglyceride levels are elevated in dengue fever and is associated with severity of dengue⁽⁷⁾.

CONCLUSIONS

Low CRP, ESR, HDL and LDL cholesterol are seen in dengue but no significant association with severity of disease. Ferritin more than 1000 and Triglyceride more than 200 is significantly associated with severity of dengue

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