

Study of clinical progression and serum ferritin level in paediatric dengue fever patients

Syed Aafaq Zishan Abid^{1*}, Suhas G Kumbhar²

¹Post Graduate Student, ²Professor, Department of Paediatrics, Bharati Vidyapeeth (Deemed To Be University) Medical College And Hospital Sangli, INDIA.

Email: aafaqsyed@gmail.com

Abstract

Background: Dengue virus (DENV) is a *flavivirus* (a genus of single-stranded non segmented RNA viruses), and is transmitted to human beings by the bite of *Aedes* mosquitoes. It is an acute infectious viral disease, also known as break bone fever. It is endemic in more than 100 countries. **Methods:** Prospective observational study. **Results:** 51 Dengue positive Patients were included in the present study of which 25(49.1%) Patients were between 6 to 12 years, 14 (27.4%) Patients below 5 years and 12 (23.5%) Patients were between 13 to 18 yrs. 29(56.8%) Patients were male and 22 (43.1%) female. Serum ferritin level was measured on 4th or 5th day of illness in these 51 study Patients. In which **Group A**-11 (21.5%) Patients had Serum ferritin level <250mcg/dl, **Group B**-10 (19.6%) Patients had Serum ferritin level between 250to500mcg/dl and **Group C**-30(58.8%) Patients had Serum ferritin level >500mcg/dl. In group A, only 1 patient progress to severe dengue remaining other recovered 10(19.6%) patients. In Group B, 1 patient progress to dengue with warning sign and 2 Patients progress to severe dengue and others recovered 7(13.7%) Patients. In group C, remaining all Patients progress to dengue with warning sign 14(27.4%) Patients and severe dengue 16(31.3%) Patients. So above results was found to be statistically significant in group C as compare to group A and B. **Conclusion:** “High serum ferritin level (>500mcg/dl) was associated with more severe form of Dengue infection (Dengue with warning sign and Severe dengue) in our study”.

Key words: Dengue fever, Severe Dengue and Serum Ferritin.

*Address for Correspondence:

Dr Syed Aafaq Zishan Abid, Bharati Vidyapeeth (deemed to be university) Medical College and Hospital Sangli, INDIA.

Email: aafaqsyed@gmail.com

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INTRODUCTION

Dengue virus (DENV) is a *flavivirus* (a genus of single-stranded non segmented RNA viruses), and is transmitted to human beings by the bite of *Aedes* mosquitoes. It is an acute infectious viral disease, also known as break bone fever. It is endemic in more than 100 countries. It is caused by 5 serotypes of Dengue virus namely DENV1, DENV2,

DENV3, DENV4, DENV5, which are genetically and antigenically different^{1,2}. DENV 1 and DENV-3 are less dangerous than DENV2 and DENV4, out of which type 4 is less virulent than type 2. Infection with one dengue serotype confers lifelong immunity to that serotype but may result in an increased risk of complications if subsequently infected with another serotype. It constitutes a major cause of pediatric morbidity and mortality in South East Asian countries. It has become a major public health problem in tropical and subtropical regions. In recent years, in spite of a poor/no dengue surveillance system in developing countries, the number of cases recorded and reported has increased markedly. Dengue outbreaks often are not recognized until hundreds of people are affected. Dengue fever is comprised of 3 stages: febrile, toxic, and convalescent. The febrile stage lasts 2-7 days followed by an abrupt fall to a normal or subnormal temperature. The toxic stage lasts 24-48 hours, with a final rapid clinical recovery without sequelae during

the convalescent stage. The toxic stage is the most critical period. Shortly after the rapid drop in temperature, varying degrees of circulatory disturbance develop due to plasma leakage from increased vascular permeability. As per the WHO 1997 classification, symptomatic Dengue virus infection has been classified into Dengue fever (DF), Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS)⁽³⁾. The revised WHO classification dengue in 2009 had three severity categories- 1) Dengue fever ; 2) Dengue fever with warning sign; 3) Severe dengue⁽⁴⁾. Dengue fever manifestations as biphasis fever, generalized bodyache, rash and a positive tourniquet test. Dengue fever with warning sign consist of abdominal pain or tenderness 2) Persistent vomiting 3) clinical features of three space fluid accumulation (edema, pleural effusion, and ascites) 4) mucosal bleeds, 5) hepatomegaly greater than 2 cm and 6) hemoconcentration. Severe Dengue was defined as patients having warning sign plus severe plasma leakage (lead to Shock and Fluid accumulation with respiratory distress); Severe bleeding; and Severe organ impairment like liver- AST or ALT \geq 1000, CNS-impaired consciousness and heart and other organ. These symptoms usually develop three to five days after the onset of disease around the time of defervescence. It has been hypothesized that severe dengue is caused by a cytokine storm inducing systemic inflammatory effects. The Pathophysiological mechanisms that cause this cytokine storm are not fully understood and represent an important focus for dengue infection. Ferritin is an iron storage protein complex of isoferritins produced by the reticuloendothelial (RE) system. The RE system plays a critical role in iron metabolism by processing hemoglobin from senescent red blood cells. Acute inflammation and infection induce the blockade of iron release resulting in a decreased serum iron, a virulence factor for many microorganisms. Elevated levels of Serum Ferritin, an acute-phase reactant, reflect the clinical response to deprive microorganisms of serum iron⁵⁻⁸. Since dengue with warning sign and severe dengue is more severe than dengue fever, the levels of Serum Ferritin in patients with dengue with warning sign and severe dengue may be higher than those with dengue fever⁷. We assessed Serum Ferritin levels during the entire clinical course, the febrile, toxic and convalescent stages, in children with dengue infection to predict the risk of developing severe dengue. In dengue fever, Serum Ferritin is disproportionately raise compared to any bacterial or viral infection and this elevated level corroborates with an increased risk of developing complications. Some studies showed a very strong correlation between Serum Ferritin level and severity of dengue infection⁹⁻¹¹. The occurrence of Hyperferritinemia in dengue virus infected patients is indicative for highly active disease resulting in immune

activation and coagulation disturbances. Therefore, patients with Hyperferritinemia are recommended to be monitored carefully. Many study concluded that high serum ferritin level with a cut-off value of >500 mcg/dl in confirmed DENV infection is associated with increased severity of dengue related illness in children. Ferritin levels measured at Day 4 or 5 may be a good predictor in outcome in dengue. So we have conducted this present study.

MATERIAL AND METHODS

Total 51 Patients were included in our study. This Prospective study was conducted at Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Sangli over a period of 6 months. **Approval from IEC has been taken.** A positive Rapid dengue test (NS1 Antigen and/or IgM ELISA) patients were included in study. Once confirmed, each patient were screened in detail in relation to history, general examination, systemic examination finding. All the investigation like CBC, Dengue (NS1 and/or IgM positive), SGOT, SGPT, Serum Ferritin level and other investigations were entered on proforma. Every Patient was managed according to the standard protocols of dengue fever. Serum Ferritin level of all the patients was sent to laboratory on day 4th or 5th of illness. Normal levels were defined as Serum Ferritin level up to 250 mcg/dl. Patients were follow up during their hospital stay for development of symptoms of Dengue fever with warning sign or Severe Dengue or recovery. Serum Ferritin level was measured on 4th or 5th day of illness in these 51 study Patients. In which study Patients divided into 3 groups according to Serum Ferritin level. Group A- Serum Ferritin level <250 mcg/dl. Group B- Serum Ferritin level between 251 to 500 mcg/dl. Group C- Serum Ferritin level >500 mcg/dl.

Statistical analysis: All the observational findings were recorded and entered into prestructured proform. The whole data was analysed with help of statistician by Chi sq test and p value was said to be significant (<0.05).

RESULTS

Total 51 Dengue positive Patients were included in the present study of which 25 (49.1%) Patients were between 6 to 12 yrs, 14(27.4%) Patients below 5 yrs and 12(23.5%) Patients were between 13 to 18 yrs. 29 (56.8%) Patients were male and 22(43.1%) female. Serum Ferritin level was measured on 4th or 5th day of illness in these 51 study Patients. In which study Patients divided into 3 groups according to Serum Ferritin level. Group A-11 (21.5%) Patients had Serum Ferritin level <250 mcg/dl. Group B-10 (19.6%) Patients had Serum Ferritin level between 251 to 500 mcg/dl. Group C-30 (58.8%) Patients had Serum Ferritin level >500 mcg/dl. In group A , only 1 Patient progress to Severe Dengue remaining other recovered

10(19.6%) Patients. In Group B, 1 Patient progress to Dengue with warning sign and 2 Patients progress to Severe Dengue and others recovered 7(13.7%) Patients. In group C, all Patients progress to Dengue with warning sign

14 (27.4%) Patients and Severe Dengue 16(31.3%) Patients. So above results was found to be statistically significant in Group C (p-value <0.001) as compare to group A and B.

Table 1: Age and Sex wise Distribution

| Dengue Serology test | No of patients (n= 51) |
|----------------------|------------------------|
| NS1Ag | 37 (72.5 %) |
| IgG | 10 (19.6 %) |
| IgM | 20 (39.2 %) |

Table 2: Dengue Serology Test

| Age | No of patients (n= 51) | Male (n=29) | Female(n=22) |
|-----------------|------------------------|-------------|--------------|
| 1 month - 5 yrs | 14 (27.4 %) | 5 (35.7%) | 9 (64.2%) |
| 6 - 12 years | 25 (49.1 %) | 17 (68%) | 8 (32 %) |
| 13 – 18 years | 12 (23.5 %) | 7 (58.3%) | 5 (41.6%) |

Table 3: Final Classification of Dengue

| Final Diagnosis | No of patients (n= 51) |
|---------------------------|------------------------|
| Acute dengue fever | 17 (33.3 %) |
| Dengue with warning signs | 16 (31.3 %) |
| Severe Dengue | 18 (35.2 %) |

Table 4: Serum Ferritin Level

| Serum Ferritin Level | No of patients (n=51) | Minimum | Maximum | Mean ± SD |
|---------------------------|-----------------------|---------|---------|--------------|
| Group A (<250 mcg/dl) | 11 (21.5 %) | 36 | 242 | 110.5 ± 57.2 |
| Group B (251- 500 mcg/dl) | 10 (19.6 %) | 254 | 478 | 337.1 ± 75.3 |
| Group C (>500 mcg/dl) | 30 (58.8 %) | 530 | 3645 | 2599 ± 878.7 |

Table 5: Comparison of serum Ferritin level and Severity of dengue

| Serum Ferritin Level | Dengue with warning signs | Severe dengue | Acute Dengue fever |
|----------------------|---------------------------|---------------------------|--------------------|
| <250 mcg/dl | 0 (0 %) | 1 (1.9 %) | 10 (19.6 %) |
| 251- 500 mcg/dl | 1 (1.9 %) | 2 (3.9 %) | 7 (13.7 %) |
| >500 mcg/dl | 14 (27.4 %) | 16 (31.3 %) | 0 (0 %) |
| | (P value <0.01) | (P value<0.001) | |

DISCUSSION

In recent years there has been a marked increase in cases of Dengue fever in south-east Asia. Currently there is no specific drug or preventive vaccine available for Dengue infection. The mainstay of management of Dengue infected patients is supportive care and close monitoring for complications¹². Most of these Patients recover within 5 to 7 days from onset of the febrile illness while only a small percentage progress to Severe Dengue¹³. Severe Dengue often occurs at the end of febrile or during convalescent stage and carries a very high mortality. It is very crucial to predict the severe form well in advance even prior to the appearance of warning signs by a simple diagnostic marker so that early identification and appropriate management would improve the outcome in these patients. In the present study we found that higher Serum Ferritin level at the time of 4th or 5th day of dengue fever was found significant associated with more severe form of dengue infection. Mean Serum Ferritin level was

significant higher in patients with Dengue with warning sign and Severe Dengue as compared to Dengue fever. In our study, Majority of our Patients were male (56.8%). A study conducted in Singapore that all dengue test positive Patients with dengue fever cases were male (71%)¹⁴. In Lahore Hospital study, majority of the Patients were also male (69.4%)¹⁵. Results from the present study showed that high Serum Ferritin level is associated with Severe Dengue which is noted in other studies as well. A study conducted during a Dengue outbreak on the Caribbean island Aruba which compared the Serum Ferritin levels in dengue infected patients with those having other viral illnesses concluded that Serum Ferritin is a useful clinical marker to differentiate Dengue from other febrile illnesses; Serum Ferritin levels >500ng/ml is associated with severe disease ; Serum Ferritin levels measured on day 4-5 better predicts the outcome of Dengue infection and it concluded that these patients with Hyperferritinemia should be monitored carefully for complications¹⁶. Another study

conducted in one hundred seventy-seven Thai children which measured Serum Ferritin levels during the entire clinical course (febrile, toxic and convalescent stages) showed similar results¹⁰. In a study conducted in South India by Soundravally R *et al.*, which included 48 dengue infected cases and 48 cases with other febrile illness as controls, Serum Ferritin levels were measured on the day of admission (which is a median of 4 days after the onset of fever) and day of defervescence (which is a median of 4 days after the day of admission)⁹. The study concluded that raised Serum Ferritin levels could predict the severity of Dengue with a sensitivity and specificity of 76.9% and 83.3% respectively⁹. The current study also revealed similar results. Recently published another study by Petchiappan *et al.* (2019)¹⁶ at Tamilnadu, India also described similar finding on 119 patients with dengue fever. Evalda *et al.* (2017)¹⁷ at Indonesia described the association of high Serum Ferritin level with Dengue shock syndrome in children. Our study is unique in that Serum Ferritin was measured once at the time 4th or 5th day of Dengue infection whereas in most of the earlier studies Serum Ferritin levels were done at multiple times during various stages of clinical illness⁹⁻¹¹. The results of the present study in which Serum Ferritin was measured either at the time of 4th or 5th day of dengue infection within 7 days from onset of fever, correlated with the findings of the previous studies. It would be simpler, easier and convenient to measure Serum Ferritin on a single day, which is practically feasible in clinical setting catering to a large population.

CONCLUSION

At end point of my study, Higher Serum Ferritin level (>500mcg/dl) on 4th or 5th day of acute dengue infection was associated with more Severe form on follow up in hospital.

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