

Original Research Article

Comparative study of serum ferritin levels and hepatic transaminases between uncomplicated paediatric dengue inpatients and other febrile illnesses in Kanchipuram, India

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ABSTRACT

Background: Fever is the most common complaint with bringing children for hospital consultation. Dengue is a cause of public health concern with case fatality rate of 1%. Ferritin is an acute-phase reactant which is produced in response to infection and inflammation. Liver enzymes are also considered as markers of febrile illness. Aim of this study was to assess serum ferritin levels, aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) levels in pediatric inpatients with febrile illness, to correlate it with patient's Dengue profile and to analyse these parameters with sub-group analysis of dengue and OFI.

Methods: Among 120 children admitted for fever of more than 3 days duration were included in the study. 58 were Dengue-NS1 positive and the remaining 62 were considered to be OFI. Serum ferritin levels, AST and ALT were the investigative parameters measured at the time of admission for the study and treated as per WHO Dengue Guidelines. Data was coded and entered in Microsoft Excel 2013. Data was analysed using SPSS v16. p value of <0.05 was considered statistically significant.

Results: Ferritin levels were higher in Dengue-IgM positive subgroup than in OFI subgroup (U= 173, Z score -6.09, p<0.00001). AST levels are higher in Dengue-NS1 positive subgroup than in OFI subgroup (U= 103, Z score -8.08, p<0.00001). ALT levels were also higher in Dengue-IgM positive subgroup than in OFI subgroup (U= 377.5, Z score -4.86, p<0.00001). ALT levels are higher in Dengue-NS1 positive subgroup than in OFI subgroup (U=76, Z score -8.95, p<0.00001) as well as in Dengue-IgM positive subgroup than in OFI subgroup (U= 417, Z score -4.4, p<0.00001).

Conclusions: Hyperferritinemia and elevation of hepatic-transaminases is seen in dengue. Although elevated in other febrile illnesses, it is elevated more so in dengue. This can be a predictor of severity of dengue fever, but needs to be confirmed in larger studies.

Keywords: Fever, Dengue, Hyperferritinemia, Hepatic transaminases

INTRODUCTION

Fever is the most common complaint with which parents bring their child for a consultation to the hospital. The percentage of outpatient consultation for fever varies between 15-25% while that of emergency room

consultation is 25-35% worldwide.¹ In children, fever is an objective sign of infections produced through actions of pyrogens on thermoregulatory centres of hypothalamus. It may be accompanied by signs such as tachycardia, hypotension, poor skin perfusion, altered level of consciousness. While some fevers manifest with

mild symptoms that can be managed on an out-patient basis, others require hospital admission into a paediatric unit with some requiring intensive care.

Dengue fever is an arboviral fever caused by 5 serotypes of Dengue virus namely DENV1, DENV2, DENV3, DENV4, DENV5.² It is transmitted to human beings by the bite of *Aedes* mosquitoes.³ It is both a dreaded and dangerous arboviral infection of humans. Although there are other arboviral diseases present in India, dengue fever remains the most common cause of arboviral epidemic outbreak. With a case fatality rate of 1% overall and 3-5% in certain sections of rural India.⁴ dengue fever is a cause of public health concern. The mechanism of manifestation of clinical features in dengue fever can be explained by endothelial damage and capillary leakage due to increased capillary permeability.⁵

The clinical spectrum of dengue fever varies from mild forms characterized by mild fever with rash to dengue fever with warning signs. The warning signs are mucosal bleed, skin rash, nausea, vomiting, abdominal pain, hepatomegaly).⁶ Severe dengue fever which is characterized by severe thrombocytopenia accompanied with significant bleeding, plasma leakage which in turn can cause pedal edema, ascites, pleural effusion, respiratory distress and Multi-Organ Dysfunction Syndrome (MODS).⁷

Prior studies have identified various biomarkers for immune and endothelial cell activation as a predictor of the severity of dengue. Ferritin is an acute-phase reactant which is produced by reticulo-endothelial cells as a response to infection and inflammation.⁸ In general, ferritin levels are increased in inflammatory conditions, but studies have shown that ferritin levels were much higher in dengue virus infected patients. A study conducted by Van de Weg CA et al, during an outbreak in Aruba showed that increased ferritin levels were associated with coagulation disturbances and clinical severity of the disease.⁹ Another study by Soundravalli R et al. showed that serum ferritin levels were elevated in dengue fever higher than in other febrile illnesses.¹⁰

Liver enzymes are also considered to be a marker of severity of a febrile illness. Hepatotropic viruses are known to cause deranged Liver function tests but deranged liver enzyme profile is seen in non-hepatic infectious etiologies also.¹¹ There are very few studies comparing serum ferritin levels and hepatic transaminase levels between Dengue patients and those of Other Febrile Illnesses (OFI) in Indian population.

Aim and objectives

- To identify dengue patients among pediatric inpatients admitted with febrile illness
- To assess serum ferritin levels, Aspartate aminotransferase (AST) and Alanine

Aminotransferase (ALT) levels in pediatric inpatients admitted with febrile illness

- To correlate serum ferritin levels, Aspartate aminotransferase (AST) and Alanine Aminotransferase (ALT) levels with inpatient's Dengue IgM antibody profile and patient's hematological profile
- To analyse these parameters with sub-group analysis of Dengue and Other Febrile Illness (OFI).

METHODS

The study followed the principles of the Helsinki Declaration and ethical committee approval was obtained. The study was conducted as a prospective comparative study at Department of Paediatrics, Meenakshi Medical College Hospital and Research Institute, Kanchipuram in 120 children aged between 3-15 years of age between August and November 2019. 58 patients who were diagnosed with dengue and 62 patients who had Other Febrile Illnesses (OFI) were included in the study. Children who were admitted for fever of more than 3 days duration and Dengue NS1 antigen positive were considered to be Dengue patients and included in the dengue sub-group. These patients were treated as per the WHO Dengue Guidelines.¹² Dengue NS1 antigen negative children were included in the OFI subgroup and were investigated and treated symptomatically. In both sub-groups, Total Count (TLC), Platelet Count (Plt), Hematocrit (PCV), Serum Ferritin levels, Aspartate aminotransferase (AST) and Alanine Aminotransferase (ALT) were the investigative parameters measured at the time of admission for the purpose of the study. Urine output was also monitored after admission as per protocol and expressed in terms of urine output per ml/kg/hr. Children who were managed as an outpatient, children with duration of fever less than 3 days, more than 8 days of fever, children who were in shock and who presented with warning signs were excluded from the study. Patients diagnosed with Viral Hepatitis were also excluded from the study and those who were on treatment for anemia up to 6 months prior to the illness were also excluded from the study. Data was coded and tabulated into Microsoft Excel 2013. Statistical tests used were descriptive statistics, Pearson's Correlation, Mann Whitney U Test by using SPSS v16. A p value of <0.05 was considered to be statistically significant.

RESULTS

The mean age of the study population was 9.02±3.07 years. Out of the study population, 71 were male and the remaining 49 were female. 58 children were diagnosed as dengue fever and the remaining 62 were considered in the OFI subgroup.

Table 1 summarizes characteristics of the study population.

Table 1: Characteristics of study population.

| Parameter (units) | Mean±SD |
|---|----------------|
| Age (years) | 9.02±3.07 |
| Duration of fever (days) | 4.77±1.55 |
| Systolic blood pressure (mmHg) | 93.05±8.81 |
| Diastolic blood pressure (mmHg) | 59.32±6.88 |
| Urine output (ml/kg/hr) | 2.72±0.7 |
| Total count (cells/mm ³) | 5113±1914.2 |
| Platelet count (cells/mm ³) | 100528.2±79057 |
| Hematocrit (%) | 38.9±8.1 |

The mean ferritin level in the study population was 4815.86±5000.88 ng/dl. The mean AST level in the study population is 185.19±122.53 IU/ml. The mean ALT level in the study population was 156.3±112.13 IU/ml.

In the study population, there were statistically significant negative associations noted between platelet count and serum ferritin levels ($r = -0.57$, $p < 0.00001$); platelet count

and AST levels ($r = -0.61$, $p < 0.00001$); platelet count and ALT levels ($r = 0.63$, $p < 0.00001$).

There were also associations noted between hematocrit and serum ferritin levels ($r = 0.85$, $p < 0.00001$), hematocrit and AST levels ($r = 0.79$, $p < 0.00001$) as well as between hematocrit and ALT levels ($r = 0.75$, $p < 0.00001$).

The study population was subdivided into subgroups for further analysis. The subgroups are comprised of:

- Dengue NS1 positive Sub-group (Comprising of Cases which were Dengue NS1 positive)
- Dengue IgM Positive Sub-group (Comprising of Cases which were Dengue IgM positive)
- Other Febrile Illnesses Sub-group (Comprising of Cases which were Dengue NS1 Negative).

Table 2 depicts the mean values of Serum ferritin, AST, ALT in the different sub-groups.

Table 2: Mean values of parameters assessed in different subgroups.

| | Serum ferritin (ng/dl) | | Aspartate aminotransferase (AST) (IU/ml) | | Alanine aminotransferase (ALT) (IU/ml) | |
|--------------|------------------------|---------|--|-------|--|-------|
| | Mean | SD | Mean | SD | Mean | SD |
| Dengue NS1 + | 9267.39 | 3405.03 | 294.55 | 50.47 | 254.71 | 60.03 |
| Dengue IgM + | 10976.81 | 1962.50 | 304.5 | 45.80 | 256.86 | 58.01 |
| OFI | 511.38 | 264.24 | 79.48 | 64.77 | 61.1 | 51.87 |

In the dengue NS1 positive subgroup, there were associations between hematocrit and serum ferritin levels ($r = 0.29$, $p = 0.03$) hematocrit and AST levels ($r = 0.28$, $p = 0.04$) as well as between hematocrit and ALT levels ($r = 0.29$, $p = 0.04$). These associations were statistically significant.

In the dengue IgM positive subgroup, there were associations between hematocrit and serum ferritin levels ($r = 0.298$, $p = 0.3$) hematocrit and AST levels ($r = 0.31$, $p = 0.15$) as well as between hematocrit and ALT levels ($r = 0.22$, $p = 0.31$). However, these associations were not statistically significant.

In the OFI subgroup, there was a statistically significant association between hematocrit and AST levels ($r = 0.312$, $p = 0.01$).

Associations between hematocrit and Serum ferritin ($r = 0.14$, $p = 0.25$) as well as between hematocrit and ALT levels ($r = 0.22$, $p = 0.31$). However, these associations were not statistically significant.

The sub-groups were compared using Mann-Whitney U test to study the difference.

Table 3 compares serum ferritin levels between Dengue NS1 positive and OFI sub-groups. Ferritin levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U = 0$, Z score -9.36) and is statistically significant ($p < 0.00001$).

Table 4 compares AST levels between Dengue NS1 positive and OFI sub-groups. AST levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U = 103$, Z score -8.08) and is statistically significant ($p < 0.00001$).

Table 5 compares ALT levels between Dengue NS1 positive and OFI sub-groups.

ALT levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U = 76$, Z score -8.95) and is statistically significant ($p < 0.00001$).

Table 6 compares serum ferritin levels between Dengue IgM positive and OFI sub-groups.

Ferritin levels are higher in Dengue IgM positive subgroup than in OFI subgroup ($U = 173$, Z score -6.09) and is statistically significant ($p < 0.00001$).

Table 3: Comparison of serum ferritin levels between dengue NS1 subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean ferritin (ng/dl) | SD ferritin (ng/dl) | U value | Z Score | p value |
|--------------|----|-----------------------|---------------------|---------|---------|----------|
| Dengue NS1 + | 58 | 9267.396552 | 3405.032 | 0 | -9.36 | <0.00001 |
| OFI | 62 | 511.3833333 | 264.2097 | | | |

Table 4: Comparison of AST levels between dengue NS1 subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean AST (IU/ml) | SD AST (IU/ml) | U value | Z Score | p value |
|--------------|----|------------------|----------------|---------|---------|----------|
| Dengue NS1 + | 58 | 294.5517241 | 50.47222 | 103 | -8.08 | <0.00001 |
| OFI | 62 | 79.48333333 | 64.77327 | | | |

Table 5: Comparison of ALT levels between dengue NS1 subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean ALT (IU/ml) | SD ALT (IU/ml) | U value | Z Score | p value |
|--------------|----|------------------|----------------|---------|---------|----------|
| Dengue NS1 + | 58 | 254.7 | 60 | 76 | -8.95 | <0.00001 |
| OFI | 62 | 61.1 | 51 | | | |

Table 6: Comparison of serum ferritin levels between dengue IgM subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean ferritin (ng/dl) | SD ferritin (ng/dl) | U Value | Z Score | p value |
|--------------|----|-----------------------|---------------------|---------|---------|----------|
| Dengue IgM + | 22 | 10976.81818 | 1962.509 | 173 | -6.09 | <0.00001 |
| OFI | 62 | 3403.14 | 4375.17 | | | |

Table 7: Comparison of AST levels between dengue IgM subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean AST (IU/ml) | SD AST(IU/ml) | U Value | Z Score | p value |
|--------------|----|------------------|---------------|---------|---------|----------|
| Dengue IgM + | 22 | 304.5 | 45.8 | 377.5 | -4.86 | <0.00001 |
| OFI | 62 | 157.8 | 118.2 | | | |

Table 8: Comparison of ALT levels between dengue IgM subgroup and OFI sub-group by Mann Whitney U test.

| | n | Mean SGPT (IU/ml) | SD SGPT (IU/ml) | U Value | Z Score | p value |
|--------------|----|-------------------|-----------------|---------|---------|----------|
| Dengue IgM + | 22 | 256.8 | 58 | 417 | -4.4 | <0.00001 |
| OFI | 62 | 133.2 | 108 | | | |

Table 7 compares AST levels between Dengue IgM positive and OFI sub-groups. AST levels are higher in Dengue IgM positive subgroup than in OFI subgroup (U= 377.5, Z score -4.86) and is statistically significant (p<0.00001).

Table 8 compares ALT levels between Dengue IgM positive and OFI sub-groups. ALT levels are higher in Dengue IgM positive subgroup than in OFI subgroup (U= 417, Z score -4.4) and is statistically significant (p<0.00001).

DISCUSSION

The management for dengue fever is by symptomatic and supportive treatment. At present, there is no drug available for treatment of dengue and a vaccine against dengue is currently on trial. The diagnosis of Dengue fever is commonly performed by J Mithra Micro ELISA

kit.¹³ Dengue NS1 antigen can be detected positive between Day 1 and Day 6 of illness, while Dengue IgM Antibodies can be detected from Day 5 of illness onwards. Although considered as a standardized technique for diagnosis, the J Mithra Micro ELISA kit has its limitations with NS1 antigen sensitivity of 96% and specificity of 98, Dengue IgM/Dengue IgG sensitivity of 96% and specificity of 98%, thus having a potential to miss a diagnosis. In our study, serum ferritin levels were elevated in all 58 patients who were Dengue NS1 positive. Ferritin levels were also increased in 57 out of 62 patients with OFI. While prior studies by Soundaravalli et al, and Van de Weg CA et al, showed hyperferritinemia in severe dengue, in our study all patients with dengue had hyperferritinemia. These patients had uncomplicated dengue and did not have any complications. This result can be attributed to the small sample size. 57 out of 62 patients (91.9%) with OFI also had elevated serum ferritin. This can be attributed to

serum ferritin being elevated as an acute phase reactant. A study by Seoung Eun Kim et al has shown the efficacy of use of serum ferritin in distinguishing infectious and non-infectious etiology.¹⁴ The elevation of serum ferritin is attributed to the property of it being an acute phase reactant. There was an association between serum ferritin levels and Dengue IgM status of the patient. This can be explained as ferritin is an acute phase reactant and its production is increased with activation of both T-cells and B-cells which get activated during antibody production.¹⁵

In the dengue NS1 positive subgroup, there were associations between hematocrit and serum ferritin levels ($r=0.29$, $p=0.03$) hematocrit and AST levels ($r=0.28$, $p=0.04$) as well as between hematocrit and ALT levels ($r=0.29$, $p=0.04$). These associations were statistically significant. These findings can be attributed to the natural history of dengue fever and the findings are in line with that of previous studies.

In this study, ferritin levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U=0$, Z score -9.36) and is statistically significant ($p<0.00001$). While the studies conducted by Soundaravalli et al and Van de Weg CA et al, had a similar result in severe dengue, our study has got similar results even in uncomplicated dengue.

Ferritin levels were higher in Dengue IgM positive subgroup than in OFI subgroup ($U=173$, Z score -6.09) and is statistically significant ($p<0.00001$). Comparing the U values and Z scores between the Dengue NS1 Positive subgroup and the Dengue IgM subgroup, it shows that ferritin is elevated to a higher extent in Dengue IgM positive subgroup.

AST levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U=103$, Z score -8.08) and is statistically significant ($p<0.00001$). AST levels were also higher in Dengue IgM positive subgroup than in OFI subgroup ($U=377.5$, Z score -4.86) and is statistically significant ($p<0.00001$). This finding can be attributed to a transient rise in liver enzymes in dengue fever. Comparing the U values and Z scores between the Dengue NS1 Positive subgroup and the Dengue IgM subgroup, it shows that AST is elevated to a higher extent in Dengue IgM positive subgroup.

ALT levels are higher in Dengue NS1 positive subgroup than in OFI subgroup ($U=76$, Z score -8.95), statistically significant ($p<0.00001$) as well as in dengue IgM positive subgroup than in OFI subgroup ($U=417$, Z score -4.4) and statistically significant ($p<0.00001$). This finding can be reasoned to a transient rise in liver enzymes in dengue fever. Through a comparison of the U values and Z scores between the Dengue NS1 Positive subgroup and the Dengue IgM subgroup, it is seen that ALT is elevated to a higher extent in Dengue IgM positive subgroup.

However, the findings of this study cannot be generalized due to a small sample size of 120 children. Moreover, the study population from Kanchipuram cannot be generalized to the entire Indian population. Also, our study assessed serum ferritin levels, serum AST and serum ALT levels at admission and included children with uncomplicated dengue. There is a need for further studies including cases of severe dengue with complications to assess the role of ferritin and hepatic aminotransferases as a marker of prediction of severity.

CONCLUSION

Hyperferritinemia and elevation of hepatic transaminases is seen in Dengue fever. While these are also elevated in other febrile illnesses, it is elevated more so in dengue fever. There is a potential for serum ferritin levels and these hepatic transaminases to be used as a marker for diagnosis of dengue fever and in prediction of the severity of dengue fever, but needs to be confirmed in larger studies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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