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Hyperferritinemia in uncomplicated pediatric dengue patients in Kanchipuram, Tamil Nadu, India

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Background: Dengue fever is an arboviral fever caused by 5 serotypes of Dengue Virus DENV1-5. Ferritin is an acute-phase reactant and produced by reticuloendothelial cells in response to inflammation and infection. Studies have shown that ferritin is a predictor of the severity of dengue. **Aim:** The objectives of this study were to assess serum ferritin levels in pediatric dengue patients, correlate it with the patient's dengue antibody profile (Dengue IgM and IgG) and to correlate it with the hematological profile in pediatric dengue patients. **Methodology:** 58 Children who were admitted for fever of more than 3 days duration and Dengue NS1 antigen positive were included in the study. In these children; Total Count (TLC), Platelet Count (Plt), Hematocrit (PCV), Serum Ferritin levels were the investigative parameters measured at the time of admission for the purpose of the study. **Results**: The mean age of the study population was 8.51±3.5 years. All 58 children had elevated serum ferritin levels. The mean serum ferritin levels in the study population as a whole were 8762.224±3556.09 µg/ml. The mean serum ferritin levels in children who were Dengue IgM negative was 7031.78±2669.44 µg/ml. **Conclusions:** Hyperferritinemia is seen in dengue fever and is associated with the Dengue IgM status of the child. There is a potential for serum ferritin levels to be used as a marker for diagnosis of dengue fever and in the prediction of the severity of dengue fever but needs to be confirmed in larger studies.

Keywords: Dengue fever, Hematological profile, Hyperferritinemia

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Introduction

Dengue fever is an arboviral fever caused by the dengue virus. It is caused by 5 serotypes of Dengue virus namely DENV1, DENV2, DENV3, DENV4, DENV5, and is transmitted to human beings by the bite of Aedes mosquitoes [1,2]. It is the most important arboviral infection of humans. Other arboviral diseases present in India include Japanese Encephalitis [3], Chikungunya [4], and Kyasanur Forest Disease [5] but dengue fever remains the most common cause of the arboviral epidemic outbreak.

The case fatality rate of dengue is 1% while the fatality rate is as high as 3-5% in certain sections of rural India [6]. The clinical features of dengue fever can be explained by endothelial damage and capillary leakage due to increased capillary permeability [7]. There is also cytokine stimulation during dengue.

The clinical spectrum of dengue fever varies from mild forms characterized by mild fever with rash, dengue fever with warning signs (mucosal bleed, skin rash, nausea, vomiting, abdominal pain, hepatomegaly) [8]. Severe dengue fever which is characterized by severe thrombocytopenia accompanied with significant bleeding, plasma leakage which in turn causes fluid accumulation (as pedal edema, ascites or pleural effusion), respiratory distress, and Multi-Organ Dysfunction Syndrome (MODS) [9].

Previous 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 and produced by reticuloendothelial cells in response to inflammation and infection [10]. 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. [11] during an outbreak in Aruba has shown that the presence of hyperferritinemia (ferritin levels≥500 µg/L) was associated with markers of immune activation and coagulation disturbances and clinical disease severity, suggesting that it could serve as a marker of the activity of the disease. An Indian study was undertaken by Soundravalli R et al [12] showed that serum ferritin levels were elevated in dengue fever higher than in other febrile illnesses.

However, there are no studies correlating serum ferritin levels with the Dengue Antibody profile in pediatric patients in India.

Aims

The objectives of this study were:

01. To assess serum ferritin levels in pediatric dengue patients
02. To correlate serum ferritin levels with patient's dengue antibody profile (Dengue IgM and IgG)
03. To correlate serum ferritin levels with the hematological profile in pediatric dengue patients

Methodology

Study period and type of study: The study was conducted at Meenakshi Medical College Hospital and Research Institute, Kanchipuram as a prospective study for 4 months between August and November 2019 in 58 children aged between 3-15 years of age who had dengue fever.

Sampling: The children were recruited for the study by convenience sampling method.

Inclusion criteria: Children who were admitted for fever of more than 3days duration and Dengue NS1 antigen positive were included in the study. In these children; Total Count (TLC), Platelet Count (Plt), Hematocrit (PCV), Serum Ferritin levels were the investigative parameters measured at the time of admission for the purpose of the study. Urine output was also calculated for the first 24 hours after admission and expressed in terms of urine output per ml/kg/hr.

Exclusion criteria: Children who were managed as an outpatient, children with the 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. Children who were on treatment for anemia up to 6 months prior to the illness were also excluded from the study. The patients were treated as per the WHO Dengue Guidelines [13]. The study followed the principles of the Helsinki Declaration and ethical committee approval was obtained. Data were coded and tabulated into Microsoft Excel 2013.

Statistical analysis: Statistical tests employed were descriptive statistics, Pearson's Correlation by using SPSS v16. The p-value of <0.05 was considered to be statistically significant.

Results

The mean age of the study population was 8.51±3.5 years. Out of the 58 children included in the study, 32 were male and the remaining 26 were female. The mean duration of fever of the children admitted was 5.8±0.7 days.

Table-1: summarizes the characteristics of the study population.

Table -1 Characteristics of Study Population		
Sl No.	Parameter (units)	Mean ± SD
1	Age (years)	8.51±3.5
2	Duration of fever (Days)	5.8±0.7
3	Systolic Blood Pressure (mmHg)	92.7 ± 9.4
4	Diastolic Blood Pressure (mmHg)	58.4 ± 8.3
5	Pulse Pressure (mmHg)	34.24 ± 13.4
6	Urine Output (ml/kg/hr)	2.95 ± 0.2
7	Total Count (cells/mm3)	3560 ± 1164.2
8	Platelet count (cells/mm3)	46166 ± 16491
9	Hematocrit (%)	45.45 ± 4.58

25 out of the 58 children (43.1%) included in the study were Dengue IgM positive. 3 out of the 58 children (5.1%) included in the study were Dengue IgG positive. All 58 children had elevated serum ferritin levels. The mean serum ferritin levels in the study population as a whole were 8762.224 ± 3556.09 µg/ml. The mean serum ferritin levels in children who were Dengue IgM negative was7031.78 ± 2669.44 µg/ml. The mean serum ferritin levels in children who were Dengue IgM negative was 10951.91 ± 3604.86 µg/ml.

There was a strong positive association between Serum Ferritin levels and Dengue IgM Status (r= 0.53, p=0.000029). There was no association noted between the Serum ferritin levels and Dengue IgG status. A significant negative association was also noted between Serum ferritin levels and Total count (r= -0.3, p= 0.02) as well as between serum ferritin and Hematocrit (r= 0.324, p= 0.01). No association was noted between serum ferritin levels and platelet count (r= -0.032, p= 0.5).

Discussion

The mainstay of management for dengue fever is supportive treatment and symptomatic. Currently, there is no drug available for the treatment of dengue, and the vaccine against dengue is currently on trial. The diagnosis of Dengue fever is commonly performed by the J Mithra Micro ELISA kit [14].

Dengue NS1 antigen can be detected positive between Day 1 to 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 the present study, serum ferritin levels were elevated in all 58 patients. 47% of study patients in the study done by Van de Weg CA et al. showed hyperferritinemia in severe dengue. 76.3% of study patients in the study done by Soundaravalli et al. showed hyperferritinemia in severe dengue.

While prior studies by Soundaravalli et al. and Van de Weg CA et al. showed hyperferritinemia in severe dengue, in the present study all patients had hyperferritinemia. This could be attributed to the small sample size. 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].

A significant negative association was also noted between Serum ferritin levels and Total Count (r= -0.3, p= 0.02). This can be explained as low total count seen in dengue is considered as a predictor of severity. A significant association was noted between serum ferritin and Hematocrit (r= 0.324, p= 0.01). This can also be explained since hematocrit is a predictor of severity. This shows that there is a potential for serum ferritin levels to be used as a marker for diagnosis of dengue fever and in the prediction of the severity of dengue fever.

While prior studies have shown that hyperferritinemia is seen in severe dengue, the present study shows that hyperferritinemia is prevalent in uncomplicated dengue also, thus adding to the existing knowledge of the pathophysiology of dengue fever and opening avenues for further studies in this domain.

However, the findings of this study cannot be generalized due to a small sample size of 58 children. Moreover, the study population from Kanchipuram cannot be generalized. Also, the present study assessed serum ferritin 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 as a marker of prediction of severity.

Conclusion

Hyperferritinemia is seen in dengue fever and is associated with the Dengue IgM status of the child.

What does the study add to the existing knowledge?

There is a potential for serum ferritin levels to be used as a marker for diagnosis of dengue fever and in the prediction of the severity of dengue fever but needs to be confirmed in larger studies.

Author's contributions

Dr. S Mohammed Aashiq: Jointly conceptualized study, contributed to data collection, tabulation, manuscript editing.

Dr. Prahlad Kadambi: Jointly conceptualized study, contributed to data collection, statistical analysis, manuscript writing.

Dr. L Sushanth Prabhath Reddy: Contributed to data collection, tabulation, manuscript writing.

Dr. S Chithra: Contributed to the critical analysis of study design, data collection, manuscript editing.

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