Original Article

Study of serum ferritin levels in various phases of dengue in pediatric dengue patients admitted in a tertiary hospital

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ABSTRACT

Background: 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. The aim of this study is to evaluate serum ferritin levels in various phases of dengue in pediatric dengue patients. **Methods:** A hospital-based, prospective, and observational study was done involving 30 dengue cases diagnosed by positive NS1 antigen or dengue specific serology (capture enzyme-linked immunosorbent assay). Serum ferritin was estimated by electrochemiluminescence in all three phases of dengue. Clinical and platelet count monitoring was done daily; respectively. All children classified as dengue with or without warning signs and severe dengue according to the World Health Organization guidelines on diagnosis treatment, prevention, and control of dengue, 2009. **Results:** Out of total of 30 children with mean age of the children were 7 years, and 61% were male who were majority. High serum ferritin levels were noted during critical phase. Eight children with dengue shock syndrome and one with acute respiratory distress syndrome were managed in intensive care unit as compared to non-severe dengue with statistically significant difference as p<0.05. Increase in serum ferritin is associated with severe thrombocytopenia. The mean hospital stay duration was found to be 5±3 days (mean±standard deviation). **Conclusion:** Serum ferritin levels taken on admission can serve as a reliable and cost-effective biomarker in the assessment and in predicting the severity of dengue fever. Serum ferritin levels may help in identifying an uncomplicated dengue illness, from that of patients who may require inpatient admission/intensive critical care.

Key words: Dengue fever, Dengue shock syndrome, Serum ferritin, Thrombocytopenia

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 endemic in more than 100 countries. It is caused by five serotypes of DENV, namely, DENV1, DENV2, DENV3, DENV4, and DENV5, which are genetically and antigenically different [1,2]. DENV1 and DENV3 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 [1,2]. 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 [3]. There is increase in number of cases reported in 2015 in India from 99,913 to 1,93,245 in 2021. The case fatality ratio being 0.06 in 2020 in India. The incidence and mortality of dengue is increasing but there is no appropriate treatment for dengue and only supportive treatment can be given [1,2].

Dengue fever (DF) is comprised of three stages: Febrile, critical, and recovery. The febrile stage lasts 2–7 days followed by an abrupt fall to a normal or subnormal temperature. The critical stage lasts 24–48 h, with a final rapid clinical recovery without sequelae during recovery phase. The toxic stage is the most critical period. Shortly after the rapid drop in temperature, varying degrees of circulatory disturbance develops due to plasma leakage from increased vascular permeability. As per the World Health Organization (WHO) 1997 classification, symptomatic DENV infection has been classified into DF, Dengue hemorrhagic fever (DHF), and Dengue shock syndrome (DSS). The revised WHO classification of dengue in 2009 had three severity categories: (1) DF; (2) DF with warning sign; and (3) Severe dengue [1].

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

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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 [3]. Elevated levels of serum ferritin, an acute-phase reactant, reflect the clinical response to deprive microorganisms of serum iron [4,6]. Since dengue with warning sign and severe dengue is more severe than DF, the levels of serum ferritin in patients with dengue with warning sign and severe dengue may be higher than those with DF [3,5].

Therefore, the present study was undertaken to assess Serum ferritin levels during the entire clinical course, the febrile, critical, and recovery phase, in children with dengue infection to predict the risk of developing severe dengue. The objectives of the study were to assess serum ferritin levels during the entire clinical course, the febrile critical and recovery phase, in children with dengue infection to predict the risk of developing severe dengue.

MATERIALS AND METHODS

A hospital-based, prospective, and observational study was done involving 30 dengue cases diagnosed by positive NS1 antigen or dengue specific serology (capture enzyme-linked immunosorbent assay [ELISA]). Serum ferritin was measured at all three phases of dengue by electrochemiluminescence clinical and platelet count monitoring was done daily. Blood samples were drawn on day 3, 5, and 7 of illness corresponding to the febrile, critical, and recovery phases, respectively. All children were classified as dengue with or without warning signs and severe dengue according to the WHO guidelines on diagnosis treatment, prevention, and control of dengue, 2009. The correlation between serum ferritin levels and platelet count was analyzed based on the day of illness.

Sample Selection Criteria

Children from 1 month to 18 years of age who are Dengue MAC ELISA or Dengue NS1 antigen ELISA positive with symptoms and signs of dengue illness as per the WHO guidelines, 2009 admitted to pediatric department in a tertiary Hospital, Mysore, from May 2022 to July 2022 were included in the study. Sample size of 30 was taken up for study, calculated based on standard deviation of the previous study [3]. Patients with transfusion dependent chronic anemia, malnutrition, known case of hemochromatosis, known case of hyperthyroidism and known case of leukemia were excluded from the study.

Statistical Analysis

Data collected were entered in MS Excel and analyzed using SPSS version 25.0. Descriptive statistical measures such as percentage mean standard deviation frequency were applied. Inferential statistical tests such as independent sample t-test, paired t-test, and Chi-square test were applied. Differences and associations were interpreted statistically with level of clinical significance $p<0.05$.

RESULTS

In a total number of 30 patients, 61% (n=18) were males and 39% (n=12) were females.

In a total number of 30 patients, most of them were in the age group of 6–10 years (n=11) and least number was in the age group 0–1 year (n=3). Fig. 1 represents the duration of stay of the participants enrolled in the study. The participant classified based on severity of dengue has been tabulated in Table 1. Table 2 represents the serum ferritin levels and platelet count in various phases of dengue. Finally, Fig. 2 gives a graphically representation
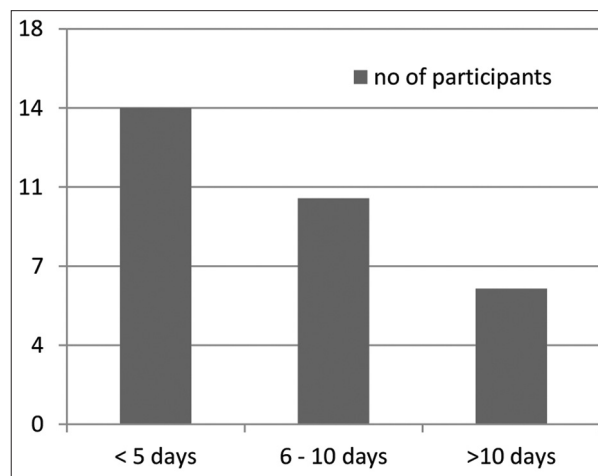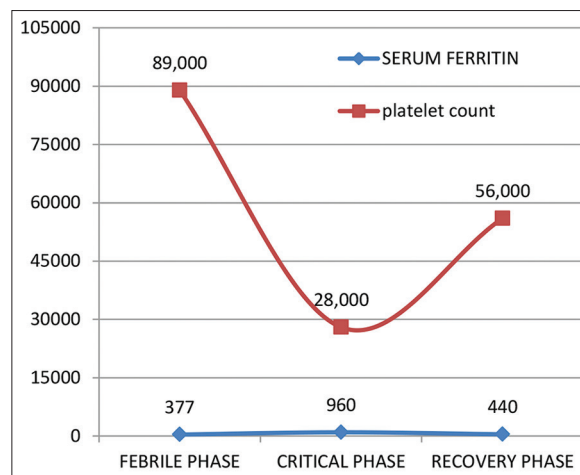

Figure 1: Duration of stay

Figure 2: Serum ferritin and platelet counts during the phases of dengue

Table 1: Participants classified based on severity of dengue

Parameters	Severe dengue	Non severe dengue
No of participants	21	09

Table 2: Serum ferritin levels and platelet count in various phases of dengue

Parameters	Febrile phase (mean)	Critical phase (mean)	Recovery phase (mean)
Serum ferritin (ng/mL)	377	960	440
Platelet count (cells/µL)	89000	28000	56000

of the serum ferritin levels and platelet levels during the progress of DF.

A total of 30 children aged between 1 month and 18 years were analyzed, of which there were 18 males (61%) and 12 (39%) females. Diagnosis of dengue infection was established by positive NS1 antigen in 19 subjects while in the remaining 11, it was diagnosed by positive dengue serology by ELISA. Out of all the total 30 subjects, only 9 (30%) subjects had clinical severe dengue, of which six were males and three females. One child had acute respiratory distress syndrome. The mean platelet count in critical phase is 42,000 cells/μL. Serum ferritin levels were measured in febrile (day 3), critical (day 5), and recovery (day 7) phases of dengue. The mean serum ferritin level in critical phase was 960 ng/mL. Significant correlation is noted in serum ferritin levels and thrombocytopenia in critical phase (p=0.012). Around 47% of the study population stayed in the hospital for ≤5 days; 33% stayed for 6–10 days; 20% stayed for >10 days. The mean day of admission of children was on day 3–4. 32% required intensive care.

DISCUSSION

Currently dengue is causing major public health concern throughout the World particularly in South East Asian countries [8]. Serum ferritin levels are elevated in patients with DF and elevated serum ferritin levels are associated with increased incidence of thrombocytopenia and increased length of hospital stay, requiring intensive care. In this study, the serum ferritin levels were high in severe compared to non-severe cases. The trend of serum ferritin levels helped in identifying the severe dengue cases. Some studies have shown a strong correlation between serum ferritin level and severity of dengue infection suggesting that hyperferritinemia should be monitored carefully [5,9,10].

There are some studies which have conflicting reports, concluding that hyperferritinemia does not correlate with severity of platelet drop [6,7]. Hence, there are controversies over role of serum ferritin in DF.

In a study conducted by Petchaiappan *et al.,* serum ferritin levels negatively correlated with the platelet count (r=0.51, p<0.001). Similarly, a case–control study conducted in Jawaharlal Institute of Postgraduate Medical Education and Research, India, compared serum ferritin, ceruloplasmin, and alpha1-antitrypsin levels of 48 dengue cases with those of 48 OFIs. They discovered significantly higher levels of ceruloplasmin and ferritin in severe dengue patients compared to non-severe dengue and OFI patients. Only ferritin had the highest sensitivity and specificity on the day of admission, with 76.9% and 83.3%, respectively, and these numbers were 90% (sensitivity) and 91.6% (specificity) around defervescence, indicating that ferritin may serve as a potential biomarker for the early prediction of disease severity. A serum ferritin level of 1200 ng/mL was found to be a predictor of DHF in children [10]. The relationship between dengue severity and serum ferritin levels, platelet count, and hematocrit varied. Among the three parameters measured, serum ferritin levels increased and platelet counts decreased as the severity of dengue increased. In another study conducted in Aruba and Brazil showed, increased levels of serum ferritin were significantly associated with disease severity in DENV infection. Higher ferritin levels were associated with higher viral copy numbers on days 2–3 of illness in dengue patients. However, no significant difference in ferritin levels was found between dengue patients with and without warning signs in this study [7]. However, in our study, serial monitoring of serum ferritin levels and thrombocytopenia helped to assess the severity and prognosis of the disease. The sampling procedure was purposeful, which limits generalizability and the selection of representative samples. As a result, the study must be conducted with a larger sample size in order to generalize the findings.

CONCLUSION

Serum ferritin levels taken on admission can serve as a reliable and cost-effective biomarker in the assessment and in predicting the severity of DF. Serum ferritin levels may help in identifying an uncomplicated dengue illness, from that of patients who may require in patient admission/intensive critical care.

REFERENCES

1. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: World Health Organization; 2009. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue [Last accessed on 2022 Apr 28].
2. Ministry of Health and Family Welfare. National Vector Borne Diseases Control Programme. New Delhi: Ministry of Health and Family Welfare, Directorate General of Health Services; 2022.
3. Abid AS, Kumbhar SG. Study of clinical progression and serum ferritin level in paediatric dengue fever patients. Medpulse Int J Paediatr 2021;18:6-9.
4. Suresh SC, Hanumanthaiah R, Ramakrishna C, Sandeep R, Narasimhasetty PS, Ramakrishna V, *et al*. Serum ferritin as a prognostic indicator in adult dengue patients. Am J Trop Med Hyg 2020;104:1072-8.
5. Prasad KN, Raj R, Chaudhary AK. Study on role of serum ferritin level as a marker in predicting the severity of dengue in children aged 5-16 years. IOSR J Dent Med Sci 2021;20:57-60.
6. Petchiappan V, Hussain TM, Thangavelu S. Can serum ferritin levels predict the severity of dengue early? An observational study. Int J Res Med Sci 2019;7:876-81.
7. William V, Menon N, Bhatia P, Biswal M, Sreedharanunni S, Rawat A, *et al*. Serum ferritin neither predicts organ dysfunction nor mortality in paediatric sepsis due to tropical infection. Front Paediatr 2020;8:607673.
8. Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health 2008;39:832-6.
9. Biswas A, Pangtey G, Devgan V, Singla P, Murthy P, Dhariwal AC, *et al*. Indian national guidelines for clinical management of dengue fever. J Indian Med Assoc 2015;113:196-206.
10. Soundravally R, Agieshkumar B, Daisy M, Sherin J, Cleetus CC. Ferritin levels predict severe dengue. Infection 2015;43:13-9.