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Prognostic significance of hyperferritinemia in dengue: A tertiary health care centre study

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Abstract

Background: Dengue infection is a major public health threat; early recognition is crucial to improve the survival in severe dengue. For prediction of dengue, various biomarkers are present but they are rarely used. We used serum ferritin to predict the severity at an earlier stage.

Methods: This is a prospective observational study conducted in a tertiary health care centre involving 200 dengue cases diagnosed by positive NS1 antigen by ELISA. Serum ferritin was measured in all at the time of diagnosis, day 3 and day 7. We monitored the patients both clinically and biochemically daily and classified them as severe and non-severe according to 2009 WHO criteria.

Results: The mean age of the patients was 34.14 ± 12.4 years. Out of 200 patients, 136 (68.0%) patients were male and rest 64 (32.0%) were females, 56 developed severe dengue. All the 200 patients had fever (100%) and arthralgia (100%). Other clinical symptoms like rash, nausea, abdominal pain, persistent vomiting, mucosal bleeding, liver enlargement, clinical fluid accumulation, dengue haemorrhagic fever, dengue shock syndrome, altered sensorium, severe plasma leakage, and patients with ALT more than 1000 U/L was reported in 108 (54.0%), 58 (29.0%), 46 (23.0%), 59 (29.5%), 32 (16.0%), 19 (9.5%), 13 (6.5%), 9 (4.5%), 35 (17.5%), 2 (1%), 12 (6.0%) and 3 (1.5%) patients respectively. The serum ferritin level was correlated with patients having rash, abdominal pain and persisting vomiting both on day 3 and day 7. A negative correlation was observed between serum ferritin level and total platelets count both on day 3 ($r = -0.2226$; $p = 0.0016$) and day 7 ($r = -0.3562$; $p = 0.0001$). Patients with severe dengue had significantly low platelet count and higher ferritin levels.

Conclusions: Elevated serum ferritin levels can be used as a potential early prognostic marker to predict the severity of dengue infection in clinical practice.

Keywords: Predictor of severity, serum ferritin, early, severe dengue

Introduction

Dengue is a systemic and dynamic disease. It is a mosquito borne tropical infection that is caused by dengue virus ^[1]. Primarily Dengue virus has four serotypes DENV1, DENV2, DENV3, DENV4. It is a RNA virus belonging to Flaviviridae. The global burden of dengue has increased at least fourfold over last three decades and there are now 1.5 Billion people at risk of the disease but the case fatality rate in dengue is only 2.5% ^[2]. Before 1970 only nine countries has experienced some dengue epidemics. But at present Dengue has affected more than 100 countries in tropical and subtropical countries. Today Dengue virus possess a major threat to global public health. The number of dengue outbreaks caused by four serotypes of dengue has increased since 1980, mainly affecting South America, Asia and the Carribean. It is transmitted primarily by the vector female *Aedes* ^[3] *aegypti* through bite. The female mosquito bites human during day time. Once infected, the mosquito remains infective for life time. Clinically severe dengue results from interplay between virus related virulence factors and host factors which include inflammatory response of the host to infection with exuberant T and B cell activation, release of cytokines (cytokine storm), altered endothelial function with increased vascular permeability and nutritional status of the host ^[4].

Dengue infections result in dramatic alterations of host physiological parameters and there could be many potential biochemical and immunological markers ^[5, 6] which might have diagnostic and prognostic value. Serum Ferritin is an acute phase protein and elevated levels of Ferritin have been associated with the pathogenesis of many inflammatory, infectious viral diseases like Hepatitis C, Dengue Fever, West Nile fever.

One study in India showed that α -1 Antitrypsin, Ceruloplasmin and Ferritin was raised in dengue fever. Serum Ferritin have longer half-life unlike the cytokines, so that it is easy to measure.

This present study was carried out with an aim to establish a relation between Serum Ferritin and the severity of Dengue fever in adult population.

Materials and Method

This is a hospital based prospective observational study conducted from January 2017 to September 2018 in a tertiary health care center i.e S.C.B Medical College, Cuttack, Odisha. All probable cases above 15 year of age with fever, aches, rash, hemorrhagic rash admitted to the Hospital were taken in to consideration.

Inclusion criteria

- Adults population of >15 years of age with fever, aches, rash, abdominal pain, vomiting.

Exclusion criteria

- Pediatric population
- Patients with chronic diseases like, Malaria, Meningitis, enteric fever, Iron deficiency anaemia, collagen vascular diseases, immunocompromised state, Multiple Blood Transfusion, Liver diseases, Diabetes melitus and malignancy
- Patients did not give consent for the study.

After obtaining patients informed consent for participation in the study, 5ml of venous blood samples was collected. NS1Ag test was carried out by ELISA methods and serum ferritin level was analysed by using electrochemiluminescence immunoassay. Serum Ferritin level was measured twice i.e. on day 3rd and on day 7th for comparison and analysis.

Total 200 patients were taken for the study who fulfill the criteria for the purpose. The severity of dengue fever was classified by clinical features and blood parameters according to WHO classification 2009 for dengue fever.

Statistical analysis

The data was entered in a predesigned excel sheet for window. The data was presented by number followed by percentage and mean followed by standard deviation etc. The comparison of mean between two groups was carried out by Mann-Whitney test. The comparison of mean of serum Ferritin level at day 3 and day 7 was compared with paired t test. The correlation coefficient was calculated between serum Ferritin level and total platelets counts of the patients. A p value < 0.05 was considered for statistical significant. All the data was analysed by using Graph-Pad Instat version 3 for window.

Results

Two hundred dengue positive confirmed patients were considered for final analysis. The mean age of the patients was 34.14±12.4 years. The age of the patients was ranging

from 15 years to 79 years. Out of 200 patients, 136 (68.0%) patients were male and rest 64 (32.0%) were females. There was no difference in the mean age of the male and females patients ($p>0.05$).

The patients were presented with various clinical signs and symptoms. All the 200 patients had fever (100%) and arthralgia (100%). Other clinical symptoms like rash, nausea, abdominal pain, persistent vomiting, mucosal bleeding, liver enlargement, clinical fluid accumulation, dengue haemorrhagic fever, dengue shock syndrome, altered sensorium, severe plasma leakage, and patients with ALT more than 1000 U/L was reported in 108 (54.0%), 58 (29.0%), 46 (23.0%), 59 (29.5%), 32 (16.0%), 19 (9.5%), 13 (6.5%), 9 (4.5%), 35 (17.5%), 2 (1%), 12 (6.0%) and 3 (1.5%) patients respectively. The distribution of patients on the basis of their clinical signs and symptoms has been illustrated in Table-1

The serum ferritin level was measured at day 3 and day 7 of each patients. The median serum ferritin level at day 3 was found to be 909 ng/mL and at day 7 was 812 ng/mL. There was no statistical significant difference in mean serum ferritin level measured at day 3 and day 7 (Paired t test, 0.7067; $p=0.4846$). The serum Ferritin level was compared in patients with and without symptoms. There was a significantly high value of serum ferritin level in patients with rash, abdominal pain and persistent vomiting in comparison to patients without these symptoms both on day 3 and day 7. The detail comparison of serum ferritin level among the patients with and without symptoms measured at day 3 and day 7 has been shown in table-2.

The serum ferritin level was correlated with total platelets level both at day 3 and day 7. A negative correlation was observed between serum ferritin level and total platelets level both at day 3 ($r=-0.2226$; $p=0.0016$) and day 7 ($p=-0.3562$; $p=0.0001$). The correlation between serum ferritin level and total platelets level both at day 3 and day 7 was presented in Figure 1 and Figure 2 respectively.

Table 1: Distribution of patients on the basis of their clinical signs and symptoms (n=200)

Presentation	No. of cases (%)
Fever	200 (100%)
Arthralgia	200 (100%)
Rash	108 (54%)
Nausea	58 (29%)
Abdominal Pain	46 (23%)
Persistent Vomiting	59 (29.5%)
Mucosal Bleeding	32(16%)
Liver Enlargement >2cm	19 (9.5%)
Clinical Fluid Accumulation	13 (6.5%)
Dengue Haemorrhagic Fever	9 (4.5%)
Dengue Shock Syndrome	35 (17.5%)
Altered Sensorium	2 (1%)
ALT>1000	3 (1.5%)
Severe Plasma Leakage	12 (6%)

Table 2: Comparison of serum ferritin level among the patients with and without symptoms measured at day 3 and day 7.

Clinical symptoms	Serum Ferritin (ng/mL) (Day 3)		P value	Serum Ferritin (ng/mL) (Day 7)		P value
	Present	Absent		Present	Absent	
Rash	1778.4±1802.3	988.5±756.3	0.0001	1766.3±1917.8	967.9±844.4	0.0001
Abdominal pain	2047.6±1804.8	1217.8±1289.1	0.0001	2020.8±2075.5	1193.1±1323.3	0.0001
Persistent vomiting	2031.9±1785.2	1172.8±1234.9	0.0001	1973.1±1873.6	1177.1±1379.	0.0001

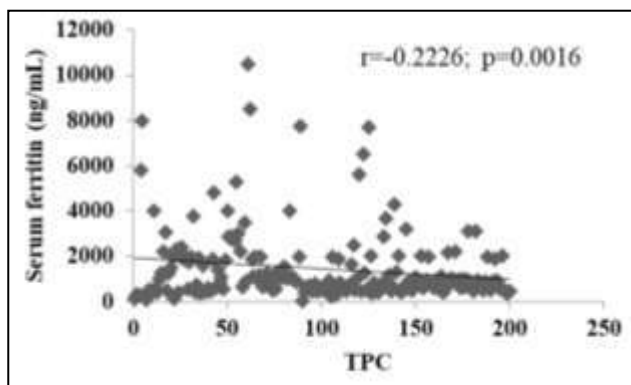


Fig 1: Correlation between serum ferritin level and total platelets level at day 3

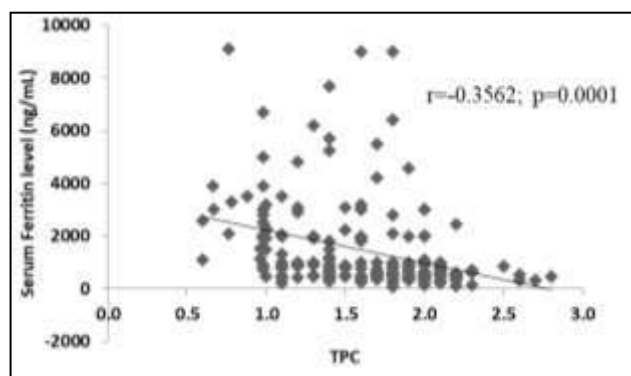


Fig 2: Correlation between serum ferritin level and total platelets level at day 7

Discussion

A total of 200 patients were Dengue positive were considered in this study. Out of 200 patients, majority were males (136 males and 64 females). In a study conducted in Singapore showed that among all PCR positive Dengue fever cases 71% were male [12]. Thai *et al.* [10], in 2011 found that mostly young adults were affected with dengue fever. In male 51 (37.5%) had dengue fever without warning signs, 44 (32.4%) with warning signs and 41 (30.1%) had severe dengue. In female cases 33 (51.6%) had dengue fever without warning signs, 16 (25%) with warning signs and 15 (23.4%) had severe dengue. It was seen that maximum patients had dengue fever without warning signs. Hepatomegaly 19 (9.5%), clinical fluid accumulation 13 (6.5%), severe plasma leakage 12 (6%) was seen. High ALT (>1000 IU/L) was present in 3 (1.5%) cases. There were 9 (4.5%) and 35 (17.5%) cases of dengue haemorrhagic fever and dengue shock syndrome respectively. We observed 84 (42%) patients were having dengue fever without warning signs, 60 (30%) patients with warning signs and 56 (28%) patients had severe dengue.

On day 3, the Mean serum Ferritin level in patients having rash, abdominal pain and persistent vomiting were 1778.4 ± 1802.3 , 2047.6 ± 1804.8 , 2031.9 ± 1785.2 respectively, which is significantly high compared to patients without these symptoms i.e. 988.5 ± 756.3 , 1217.8 ± 1289.1 , 1172.8 ± 1234.9 respectively. Similarly, on day 7, serum Ferritin levels were very high in patients having warning symptoms in comparison to without symptoms. The serum ferritin level was significantly high in patients having warning signs both on day 3 and day 7. These findings are in concordance with the study patients in Wathanee *et al.* (2008) in Bangkok [7]. Serum ferritin is an acute phase reactant and is

frequently elevated during inflammatory or infectious conditions. The cytokines released in severe form causes raise in cellular ferritin by induction of the H chain of ferritin both transcriptionally and post-transcriptionally. The study conducted by Soundravally *et al.* concluded that hyperferritinemia could predict the Dengue severity with sensitivity of 76.9% [6]. A study conducted in Aruva in Brazil showed that increased levels of Ferritin are significantly associated with dengue viral disease severity [11].

There was significant thrombocytopenia in patients having high serum Ferritin level. These findings are in concordance with Jyothi S *et al.* 2018 [13, 14].

Hyper-ferritinemia in dengue fever is associated with elevation of SGOT, SGPT and serum creatinine. A very strong correlation exist between 3rd day serum ferritin and SGOT ($r = 0.807$, $p < 0.001$), serum creatinine ($r = 0.592$ and $p < 0.001$) and also between 3rd day serum ferritin and SGPT ($r = 0.783$, $p < 0.001$). Similar result was also seen in the paper on dengue infection in the Aruba Islands by Brazilian and the Dutch medical researcher for rise in SGOT and SGPT [9]. Nadeem *et al.* 2016 [8], showed hyper ferritinaemia in dengue fever indicates highly active disease resulting in immune activation. There occur reactive hepatitis and ischemic insult to hepatic cell in dengue shock syndrome, which causes rise in liver enzymes. Hepatocytes are also activated by proinflammatory cytokines to produce high amount of ferritin, an acute phase protein leading to immune activation in dengue.

Conclusion

Hyperferritinemia can be used to predict the severity of Dengue and also the prognosis in Dengue patients. So patients having high levels of serum ferritin should be monitored very carefully from the very beginning.

Conflict of Interest: All the authors declared that there is no financial conflict of interest.

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