IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 6 Ser.6 (June. 2021), PP 57-60
www.iosrjournals.org

Study On Role of Serum Ferritin Levels As a Marker in Predicting the Severity of Dengue in Children Aged 5-16 Years

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Abstract
AIM - *To study the role of serum ferritin as a marker for predicting the severity of dengue in children.*
METHODS - *A hospital based prospective observational study conducted from February 2020 to January 2021 in a tertiary care center . 52 children aged between 5years and 16years who were infected with dengue either having NS1 antigen positive or Dengue IgM positive were taken . Serum ferritin was measured on alternative days and other laboratory parameters were taken into account for severity parameters alongwith clinical condition.*
RESULTS - *Out of all the total 52 subjects , only 9 (17.3%) subjects had clinical severe dengue, of which 6 were males and three female. The laboratory parameters used were Platelet count , Total count , SGOT , SGPT , S.Albumin . The mean Serum ferritin levels in children with severe dengue was 2120ng/ml as compared to 510ng/ml in non severe dengue children. It was observed that non-significantly, patients who had severe dengue had higher median serum ferritin levels from day 3 onwards as compared to non-severe dengue cases and mostly peaked at day 5th of illness.*
CONCLUSION - *The present study had shown that elevated serum ferritin levels done early during the febrile stage of the illness (3 to 7 days of illness) predict the severity of dengue.*

Date of Submission: 01-06-2021 Date of Acceptance: 14-06-2021

I. Introduction

Dengue fever is one of the world's important viral hemorrhagic fevers, most geographically widespread of the arthropod-borne viral illnesses, caused by *Arbovirus* of *Flavivirus* genus with 4 serotypes [1, 2] .

According to World Health Organization, around 50 to 100 million new infections are estimated to occur every year in more than 100 endemic countries across the world; of which around 500000 people with severe dengue require hospitalization each year and about 2.5% of those affected die.[3] The burden of the disease is so much that in the year 2012 World Health Organization classified the disease as "the most important viral disease that is transmitted by mosquitoes".[4]

It is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Four spectra of illness are seen

- Asymptomatic phase
- Acute febrile illness
- Classic dengue fever with or without hemorrhagic manifestation
- Dengue hemorrhagic fever (DHF) which includes Dengue Shock Syndrome (DSS) and expanded dengue syndrome [5].

Clinically dengue fever is suspected when acute febrile illness of 2–7 days presents with two or more than two of the following, namely, headache, retroorbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations [6]. Severe dengue is characterized by severe thrombocytopenia with major bleeding, plasma leakage resulting in fluid accumulation, respiratory distress and multi-organ dysfunction. The presence of certain *clinical warning symptoms* which help to predict the severity are bleeding, skin rash, nausea, persistent vomiting, abdominal pain,lethargy ,clinical fluid accumulation and hepatosplenomegaly .[7]

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.[8]

The incubation period is 1 – 7 days . Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted . Circulation of infection enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease.

In clinical practice, patients with dengue infection are grouped as A) those with warning signs that need intensive monitoring and aggressive management B) those without warning signs. Non-severe cases without warning signs can develop into severe dengue later during the course of illness. They are at risk of developing complications related to plasma leakage and thrombocytopenia often at the end of febrile stage of illness (third to fifth day of illness) which if unrecognized can be fatal.

Dengue fever is diagnosed by NS1 antigen reactivity by ELISA method usually for the first 5 days of fever. After that IgM detection by MAC-ELISA is used to diagnose dengue fever but IgM appears usually within 5–7 days of fever but sometimes it may take more time, even up to 12 days, to appear [9]. The sensitivity of NS1 for diagnosis gradually decreases beyond 5th day . NS1 disappears from blood much early in secondary Dengue virus infection due to presence of neutralizing antibody . In patients not previously infected with dengue virus, this IgM response is slow rising. It is 50% in 3–5 days, 80% in more than 5 days, and 99% in 10th day [10]. Furthermore, IgM dengue antibody may be nondetectable till 8th day of illness.

There are many laboratory findings which correlates with dengue . the most common hematological abnormalities during DHF and DSS are hemoconcentration , thrombocytopenia , neutropenia prolonged bleeding time and moderately decreased prothrombin level . This may be accompanied by hypoalbuminemia , mild metabolic acidosis with hyponatremia , consumption of complement and mild elevation of transaminases .

Studies had identified various biomarkers for immune and endothelial cell activation, biochemical and genetic markers to predict the severe dengue. The clinical utility of these markers is limited since measurement of these markers like soluble receptors, cytokines, growth factors, vWF; genetic profiling etc. is technically difficult and not widely available. Acute phase reactants like alpha1 anti-trypsin, ceruloplasmin and ferritin levels are elevated during dengue infection; they have a longer half-life unlike the cytokines, and it is feasible to measure their levels.[11]

Ferritin is an acute-phase reactant and expressed by cells of the reticulo-endothelial system in response to infection by dengue virus. In dengue fever, serum ferritin is disproportionately raised compared to any bacterial or viral infection and this elevated level corroborates with an increased risk of developing complications. [12]. A study from the Caribbean island Aruba concluded that ferritin can be used as a clinical marker to discriminate between dengue and other febrile illnesses [13]. 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.

In the present study, we analysed whether serum ferritin measured during early disease course can be used as a marker to indicate the severity which helps to triage and manage them appropriately. This research is intended for finding a simple, reliable and early predictor for early anticipation of Severe Dengue infection and preparedness for its management.

II. Aims And Objectives

This study was aimed to study the Role of Serum Ferritin levels as a marker in predicting the severity of Dengue in children and to predict the risk of progression to severe dengue at the earliest, by simple measurable tests like Serum ferritin levels to initiate appropriate intensive, supportive therapy.

III. Materials And Methods

This is a hospital based propspective observational study conducted from February 2020 to January 2021 in a tertiary care centre in the Department of Paediatrics ,Rajendra Institute of Medical Sciences, Ranchi , Jharkhand. All the cases registered in the study was interrogated for detailed history, clinically examined thoroughly and investigated.

All children aged between 5 year to 16 year diagnosed with dengue infection and admitted in department of Paediatrics , RIMS , Ranchi were included in this study after obtaining consent from their parents. Patients referred from any outside hospital with positive test results (NS1 or dengue serology positive) were also included.

None of the patients aged below 5 years and above 16 years were taken up for the analysis Both Patients presenting with fever in which both NS1 antigen test and dengue IgM serology test was negative and patients with chronic inflammatory conditions or diseases; iron overload status; sideroblastic anemia; thalasemia; malignancy; liver disease will be excluded from the study. Those Patients whose parents were not giving consent were also excluded from the study.

IV. Methodology:

This study is to based on collection of data from dengue infected patients fulfilling the criteria mentioned above. 2ml of blood was collected in Red vial and send to Microbiology laboratory. Diagnosis was made based on NS1 antigen test (done with J.Mitra ELISA kit) when the presentation was less than 5 days of illness or by positive dengue specific serology (dengue IgM done by dengue IgM; J.Mitra micro ELISA kit) if presented after 5 days of illness. Serum ferritin levels was measured (by electrochemiuminescence) if the presentation was less than 7 days from the onset of fever. Serum ferritin was measured either at the time of diagnosis if the diagnosis was based in the study centre or at the time of admission if patient referred from outside with positive test results (NS1 or dengue serology positive).

The clinical course of the disease and platelet count were monitored carefully on a daily basis and patients were classified as having severe and non-severe infection as per WHO 2009 criteria: classified as severe dengue when shock, respiratory distress, severe bleeding , liver damage, altered consciousness or organ impairment occur. Platelet count , Total count , SGOT , SGPT , Serum Ferritin , Serum albumin was done in all patients under the inclusion criteria.

V. Results

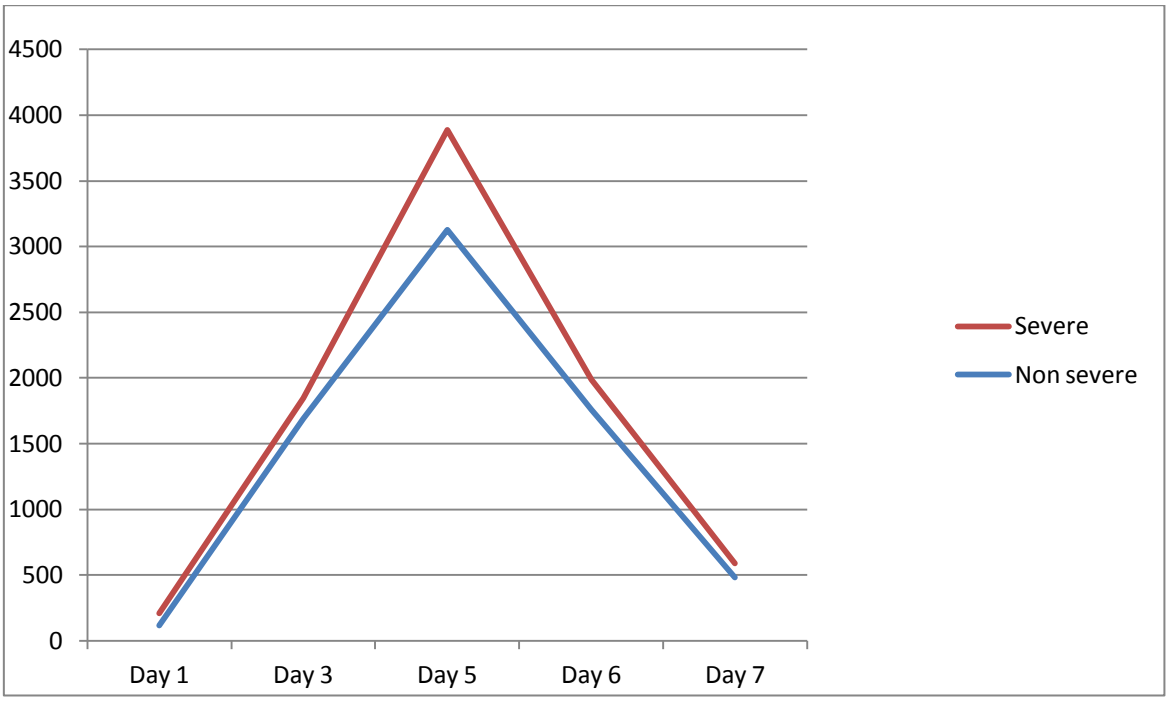
A total of 52 children aged between 5 year to 16 year were analyzed , of which there were 30 males (57.6%) and 22 (42.3%) females. Diagnosis of dengue infection was established by positive NS1 antigen in 33 subjects while in the remaining 19, it was diagnosed by positive dengue serology.

Out of all the total 52 subjects , only 9 (17.3%) subjects had clinical severe dengue, of which 6 were males and three female. Severity of dengue was determined on basis of laboratory parameters and clinically . The laboratory parameters used were Platelet count , Total count , SGOT , SGPT , S.Albumin . The mean platelet count in children with severe dengue was 16500 ×109/L whereas in non severe dengue was 90000 x 109/L. Around 20% of the study population stayed in the hospital for ≤ 3 days; 25% stayed for 4 days; 27% stayed for 5 days. Around 28% had a hospital stay for ≥7 days. Serum ferritin levels were measured in 14 subjects on day 1 , 3 ,5 ,6 and 7th day of illness. The mean Serum ferritin levels in children with severe dengue was 2120ng/ml as compared to 510ng/ml in non severe dengue children.

Table 1: Comparison of serum ferritin, platelet count, total count, S albumin, SGOT and SGPT in severe and non-severe dengue.

	Severe dengue Mean	Non severe dengue Mean
Serum ferritin (ng/ml)	2120	510
Platelet count (number/cumm)	16500	90000
Total count (number/cumm)	4200	9400
Serum Albumin (g/dl)	2.4	3.2
SGOT (U/L)	162	61
SGPT (U/L)	114	59

Serum ferritin measured from day 1 to day 7 of illness was compared in both the severe and non-severe groups and reported as line diagram . It was observed that non-significantly, patients who had severe dengue had higher median serum ferritin levels from day 3 onwards as compared to non-severe dengue cases and mostly peaked at day 5th of illness.



Comparison of serum ferritin levels in severe and non-severe dengue measured from the day 1 to day 7 of illness.

VI. Conclusion

The present study had shown that elevated serum ferritin levels done early during the febrile stage of the illness (3 to 7 days of illness) predict the severity of dengue.

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