Section: Miscellaneous

Original Research Article

INFLAMMATORY MARKERS PREDICTING THE PROGRESSION OF SEVERITY IN DENGUE

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ABSTRACT

Background: Dengue infection is a major health problem; early recognition is crucial to improve the survival in severe dengue. There are various biomarkers to predict the severity of dengue, we want to analyse whether inflammatory markers like LDH, Ferritin, Triglycerides, CRP, ESR can be used to predict the severity at an earlier stage. The aim and objective is to compare the demographic data and the levels of the inflammatory markers in non-severe group and in cases who became severe from non-severe cases. To compare the predictability of various inflammatory markers for slipping into severe dengue and to derive the cut-off values for inflammatory markers. **Materials and Methods:** We conducted a prospective analytical study for a period of 13 months, involving 25 cases in non-severe group and 26 cases in severe group with a total of 51 cases. At admission all 51 patients were of non-severe dengue and inflammatory markers and baseline investigations were sent. During the course of hospital stay 26 cases became severe dengue and 25 remained in non-severe category. The inflammatory markers sent at admission were analysed to assess whether it could predict the progression towards severity in the due course. **Result:** Out of 26 cases in severe group and 25 cases in non-severe group, demographic data was compared between the 2 groups, no significant difference($p<0.05$) was noted. ROC curve was obtained and a cut off between both the groups was derived. Cut-off of 1093ng/dl for Serum Ferritin (sensitivity of 61.5% and specificity of 56%), 2.25mg/L for CRP (sensitivity of 69.2% and specificity of 68%), 458U/L for LDH (sensitivity of 61.5% and specificity of 56%), Serum triglycerides of 174.5mg/dl (sensitivity of 53.8% and specificity of 56%), ESR of 17.55 mm/1ST hr (sensitivity of 53.8% and specificity of 64%). **Conclusion:** In our study, we could not obtain a significant difference in the levels of inflammatory markers to differentiate between the non-severe and severe groups. Diagnostic cut-off value for inflammatory markers had low sensitivity and specificity hence cannot be used to predict the progression.

INTRODUCTION

Dengue is one of the rapidly spreading mosquito-borne arboviral disease in the world. Dengue fever is transmitted by the bite of infected Aedes mosquito. Dengue virus is a small single-stranded RNA virus, belonging to Flavivirus, family Flaviviridae comprises four distinct serotypes (Dengue virus 1 to 4). Primary infection is thought to induce life long protective immunity to the infecting serotype. Dengue infection is a major health problem in tropical and subtropical countries. Efficient and accurate diagnosis of dengue is of primary importance for clinical care.[1-10]

Cytokine storms, one condition where many proinflammatory cytokines are mass-produced, might lead to cellular dysfunction in tissue/organ failures and often facilitate severe dengue disease in patients. Increased levels of IFN-γ- and TNF-α-expressing cells in liver, lung and kidney samples of post-mortem subjects evidenced a strong pro-inflammatory induction in these tissues. Co-staining of DENV RNA and IFN-γ or TNF-α using in-situ hibridization and IHC confirmed the virus-specific trigger of the pro-inflammatory response.[11-21]

Ferritin is an iron storage protein complex of isoferritins produced by reticuloendothelial (RE) system. The RE system plays a major role in iron metabolism by processing haemoglobin 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. Elevated levels of serum ferritin, an acute phase reactant, reflect the clinical response to deprive microorganisms of serum iron.[1]

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In viral infections, lipoproteins are postulated to bind to viruses, thus neutralizing their ill effects.[13,14] In our study we are studying if the levels of triglycerides can predict the progression to severe dengue.

ESR and CRP levels also may provide insight into the underlying disease process. Elevations in ESR reflect disease states that involve increased plasma protein/fibrinogen levels such as autoimmune conditions or cardiovascular disease. Increased levels of CRP generally are reflective of underlying inflammation, such as that resulting from trauma or infection.

Serum CRP level predominantly increases during the infections, tissue injuries and various pathologies. This makes CRP a potent clinical marker in various inflammatory processes.[15]

Asymmetric acute phase proteins such as fibrinogen and immunoglobulins increases the ESR.

It is thought to be a marker of vascular permeability in immune-mediated lung injury. An early increase in LDH (three times the normal value) was found to be an independent predictor of DHF.[19]

In this study, we are analysing whether inflammatory markers can predict the severity in the course of disease and to derive the cut-off value to predict the progression of the disease. To compare and see which inflammatory marker predicts the severity better. This would help us to anticipate the course of the disease and manage appropriately.

MATERIALS AND METHODS

Inclusion Criteria

1. Primary dengue infection (Ns1 and IgM positive).
2. Secondary dengue (Ns1, IgG positive or Ns1,IgM, IgG,).
3. Age group 1-14y.
4. Non-severe presentation of the disease at admission.

Exclusion Criteria

1. Dengue serology negative.
2. Other co-existing infections.
3. Other co-existing chronic inflammatory disease.

Diagnostic Criteria: The severity of DHF can be classified as severe and non-severe as mentioned in WHO 2009 guidelines. Non-severe group would include dengue with warning signs. Warning signs would include abdominal pain and tenderness, persistent vomiting, Clinical fluid accumulation, Mucosal bleed, Lethargy, restlessness, Liver enlargement >2 cm, Laboratory parameter of increase in HCT concurrent with rapid decrease in platelet count.[4]

Severe dengue includes patients with severe plasma leakage resulting in shock or fluid accumulation with respiratory distress, severe bleeding and severe organ impairment with elevated liver enzymes (SGOT and SGPT) more than 1000 IU, impaired consciousness and other organ involvement.[4]

Materials and Methods

We conducted a prospective observational study for a period of 13 months at SDM Medical College and Hospital, a tertiary care center in North Karnataka. Standard WHO defination were used to classify dengue cases as severe and non-severe. Study included children between age group of 12months to 14 years who were diagnosed as dengue with warning signs but not having severe bleeding or plasma leakage and no severe organ impairment. Data was collected and analysed from patients fulfilling the inclusion criteria, admitted in ward or PICU on day 3-5 of illness at presentation.

At admission the inflammatory markers namely Ferritin, LDH, ESR, CRP, Triglycerides and Hb, PCV, Platelets, SGOT, SGPT, Serum Albumin were sent. Patients were divided into severe and non-severe groups based on clinical prarameters and laboratory parameters during the course of hospital stay. The data was analysed to see if on admission the inflammatory markers sent can predict child going in for more severe disease.

Diagnosis was based on dengue serology (Immunochromatography assay) sent on admission. 3ml of venous blood sample was taken and investigated for Serum ferritin (Chemiluminescence Immunoassay), LDH (L to P - IFCC Ref. Proc., Calibrated), ESR(Westergren), CRP(Nephelometry), serum triglycerides (Enzymatic, end point). Consent was obtained from the patient's side for the study and data which included preliminary data and the above lab parameters with clinical diagnosis on admission was compiled in an exel sheet.

Statistical analysis: The statistical association of inflammatory markers done on admission (like serum ferritin, Triglycerides, LDH, ESR, CRP) with the progression of the disease during the course of hospital stay with a study population of 51 patients.

Levene's Test for Equality of Variances was done to compare the levels of inflammatory markers in non-severe and severe dengue.

ROC curve was derived and area under the curve was obtained. Cut-off value for inflammatory markers was obtained based on sensitivity and specificity. The software used is SPSS 22 version.

RESULTS

In our study, out of 51 non-severe cases who met the inclusion criteria were monitored for the progression of the disease 25 cases did not develop severity and 26 cases developed the severity during the course of hospital stay. Inflammatory markers were sent and Mean values of inflammatory markers in non-severe group and severe group were as follows.

Serum ferritin level of 1940.2 ng/dl and 3198.8 ng/dl, serum triglycerides of 163 mg/dl and 160mg/dl, CRP OF 5.6mg/L and 14.46, ESR of 19.5mm/1ST hr and 23.385mm/1ST hr, LDH of 1040U/L and 682.3U/L were noted in non-severe group and severe group respectively. Significant p-value ($p<0.05$) was not

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obtained for any of the inflammatory markers but a higher value was noted in serum ferritin and CRP in severe dengue compared to non-severe dengue.

Table 1

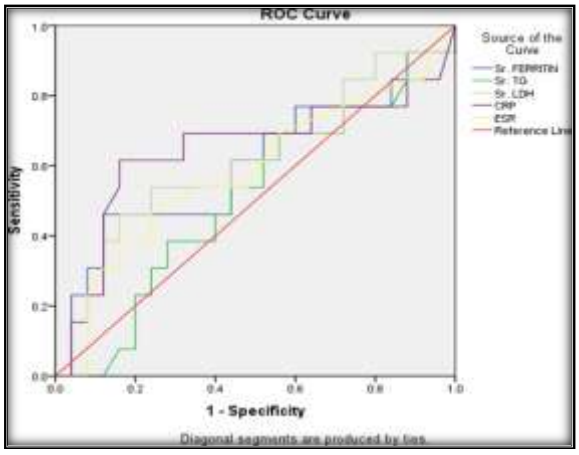
T-Test					
Group Statistics					
GROUP (NS-1, SEVERE -2)		**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
Sr. FERRITIN	1	25	1940.228	3222.5517	644.5103
	2	26	3198.769	3595.7544	705.1855
Sr. TG	1	25	163.240	70.9050	14.1810
	2	26	160.923	62.1012	12.1790
Sr. LDH	1	25	1040.800	2874.7257	574.9451
	2	26	682.308	447.8052	87.8218
CRP	1	25	5.6120	16.89933	3.37987
	2	26	14.4600	26.45573	5.18840
ESR	1	25	19.520	17.6591	3.5318
	2	26	23.385	15.8671	3.1118

Other demographic, clicical and laboratory parameters like age, fever, SGOT, SGPT, serum albumin, WBC, total duration of fever and duration of stay was compared.

Table 2

GROUP (NS-1, SEVERE -2)		**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
AGE	1	25	8.240	3.7559	.7512
	2	26	8.385	3.5222	.6908
fever	1	25	4.200	.7638	.1528
	2	26	4.462	.8593	.1685
SGOT	1	25	879.980	3631.0692	726.2138
	2	26	234.231	196.1783	38.4737
SGPT	1	25	178.148	552.5341	110.5068
	2	26	80.192	68.1027	13.3560
Sr. ALB	1	25	3.1928	.41298	.08260
	2	26	3.6792	.41133	.08067
WBC	1	25	5740.400	3438.9769	687.7954
	2	26	3942.308	2290.3734	449.1792
FEVER Total	1	25	5.560	.8206	.1641
	2	26	5.538	1.3033	.2556
DOS	1	25	5.520	.9183	.1837
	2	26	6.462	1.7716	.3474

To derive the cut-off of inflammatory markers from the data available.



The cut-off value for the inflammatory markers –

1. Serum ferritin of 1093ng/dl with sensitivity of 61.5% and specificity of 56% with AUC of 0.603 and p-value of 0.207(non-significant).
2. CRP of 2.25 mg/L with sensitivity of 69.2% and specificity of 68% with AUC of 0.645 and p-value of 0.077(non-significant).
3. Serum triglycerides of 174.5mg/dl with sensitivity of 53.8% and specificity of 56% with AUC of 0.505 and p-value of 0.955(non-significant).
4. Serum LDH of 458 U/L with sensitivity of 61.5% and specificity of 56% with AUC of 0.612 and p-value of 0.169(non-significant).
5. ESR of 17.55 mm/1ST hr with sensitivity of 53.8% and specificity of 64% with AUC of 0.585 and p-value of 0.300(non-significant).

Table 3: Area Under the Curve

Test Result Variable(s)	**Area**	**Std. Errora**	**Asymptotic Sig.b**	**Asymptotic 95% Confidence Interval**	
			Asymptotic Sig.b (p-value)	**Lower Bound**	**Upper Bound**
Sr. FERRITIN	.603	.081	.207	.444	.762
Sr. TG	.505	.083	.955	.343	.666
Sr. LDH	.612	.080	.169	.455	.770
CRP	.645	.083	.077	.483	.806
ESR	.585	.081	.300	.425	.744

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The test result variable(s): Sr. TG, CRP, ESR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

- Under the nonparametric assumption
- Null hypothesis: true area = 0.5

DISCUSSION

Dengue fever is a dynamic febrile illness that can range from a mild self-limiting form to plasma leakage, haemorrhage, or severe multiorgan dysfunction leading to severe life threatening situation. An array of mechanisms have been proposed to explain the pathogenesis of severe dengue that includes antibody-dependent enhancement [ADE] of viral infection.[7,8]

Ferritin is a reliable inflammatory marker to differentiate between dengue and fever of other origin.[6] Other studies show that serum ferritin done in febrile phase helps to predict the severity of dengue fever.[12] The presence of thrombocytopenia with concurrent haemoconcentration differentiates DHF/DSS from other diseases. In patients with no significant rise in haematocrit as a result of severe bleeding and/or early intravenous fluid therapy, demonstration of pleural effusion/ascites indicates plasma leakage.

Hypoproteinaemia/albuminaemia supports the presence of plasma leakage.[5] However hyperferritinemia in dengue illness is associated with elevation of both SGOT and SGPT, as reported in the paper on DENV infection in the Aruba Islands by the Brazilian and the Dutch medical researchers.[9]

Higher serum TG levels in severest dengue disease, and suggested that these levels can be used as prognostic markers to predict clinical outcome (van Gorpet al) (2002).[14]

CRP levels were found to be increased with suppressed platelets counts in dengue patients.[15] CRP measured in the first 3 days of illness could be a useful biomarker for early dengue risk prediction and may assist differentiating dengue from other febrile illnesses.[16]

ESR is within normal limits in most cases of dengue, independent of its clinical manifestation; this is mainly due to the hemoconcentration found in dengue patients, along with hypoalbuminaemia and hypofibrinogenemia. This contrasts with the ESR profile in patients with bacterial diseases and should be incorporated into diagnostic exclusion criteria for dengue.[17]

Serum lactate and LDH was found to be elevated in DHF and/or DSS patients.[18]

In our study, we have monitored the progression of disease in 51 cases of non-severe dengue out of which 26 became severe dengue during the course of hospital stay, 25 cases remained in the non-severe category. The inflammatory markers were sent in both the group on admission. We tried to analyse whether the Inflammatory markers sent at non-severe phase of illness can predict the cases slipping into severe category during the course of hospital stay.so as to take appropriate steps could be started earlier or monitored vigorously so that the mortatity and morbidity is decreased in dengue illness.

Hypothesis was formed that the high levels of inflammatory markers like ESR, CRP, LDH, Ferritin, Triglycerides sent on admission in non-severe dengue on day 3-5 of admission that is during early phase of illness when the children were in non-severe category could predict the children slipping into severe dengue.

We found that mean ferritin and CRP levels were higher in severe group that is 3198.7ng/dl and 14.46mg/dl compared to non-severe where it is 1940ng/dl and 5.6mg/dl respectively. But the difference was not statistically significant enough to obtain a co-relation. Cut off derived was for serum ferritin is 1093ng/dl with sensitivity of 61.2% and specificity of 56% and cut off derived for CRP is 2.25mg/L with sensitivity of 69.2% and specificity of 68% which indicated that serum ferritin and CRP is%, not effective as a prognosticating marker.

Similarly mean triglyceride level was 2874U/L and 447U/L in non-severe and severe dengue which shows that with increase in severity the levels fall. With the cut-off 458 U/L was derived with sensitivity of 61.5% and specificity of 56%, not effective as a prognosticating marker.

The levels of triglyceride and ESR in severe dengue was 160mg/dl and 23.8mm/1st hr and in non-severe dengue was 163.2 and 19.5mm/1st hr respectively. Serum triglycerides of 174.5mg/dl with sensitivity of 53.8% and specificity of 56%. ESR of 17.55 mm/1ST hr with sensitivity of 53.8% and specificity of 64%. Hence cannot be used to predict the severity.

Limitations: The limitation of the study is that the analysis involved small number of cases in both the groups. The trend of the inflammatory markers was not monitored as the disease progressed in individual patient in cases who developed severe dengue and in non-severe dengue for comparison.

The data adds to the existing literature, the inflammatory markers done at admission could not predict the progression to severe disease. Cases with dengue fever have to be closely monitored to detect the severity at the earliest.

CONCLUSION

From this study we conclude that the inflammatory markers done during early phase of illness couldnot predict the children slipping into severe dengue category.

The cut-off values for Serum Ferritin, LDH, CRP, ESR, Triglycerides obtained had low sensitivity and specificity, hence cannot be used in the clinical practise but further studies are needed to support the data.

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