Effect of Dengue on Haematological Profile and Liver Function

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ABSTRACT

BACKGROUND

Dengue is considered to be the most common arboviral disease worldwide and one of the most important emerging viral tropical diseases which affects up to 100 million people across the tropical world. Dengue infection is associated with major changes in haematological profile of the patients. Even though the liver is not the major target organ, pathological findings such as hepatocellular necrosis and inflammatory cell infiltration have been identified in liver biopsy specimens of patients with Dengue and it is reflected by the derangement in liver enzymes. Our study aims at studying the haematological changes and alterations in liver functions in patients affected by dengue.

METHODS

A total of 820 serologically confirmed cases of dengue was included in the study during the period June 2016 - December 2017. Demographic details, clinical details and Laboratory investigations such as total count, differential leukocyte count, platelet count, liver function tests were collected from medical records, entered and statistically analysed.

RESULTS

A total of 820 serologically confirmed cases of dengue were included in the study. 800 patients (97.4%) were classical DF case, 7 (1%) were DHF and 13 (1.6%) were DSS. Our study showed a of M:F ratio of 1:1.04. Dengue infection was associated with major haematologic changes such as leukopenia (56%), and thrombocytopenia (86%). In addition to the haematological changes, the disease is associated with significant alteration in liver function test such as elevation of SGPT and SGOT, hypoalbuminemia and elevation of serum bilirubin.

CONCLUSIONS

Our study shows that in addition to haematological abnormalities, dengue virus infection is associated with major derangements of liver function such elevated transaminase levels, hypoalbuminemia and hyperbilirubinemia. Leukopenia, thrombocytopenia, raised SGPT and SGOT necessitate further evaluation by testing for dengue in febrile patients in post rainy seasons so that early therapeutic measures can be initiated to reduce the morbidity and mortality.

KEYWORDS

Dengue, Shock, Transaminitis, Leukopenia, Thrombocytopenia

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BACKGROUND

The word dengue is believed to have originated from Swahili language "ki denga pepo", which describes sudden cramp like seizure. The clinical symptoms suggestive of dengue virus infection were described as early as 265-420 AD in China. Dengue has gradually evolved as one of the important causes of febrile illness in the tropical and subtropical region.[1] World health organization estimates that about 50 - 100 million of world populations become infected yearly, and among them 500,000 are DHF with 22,000 deaths.[1,2]

Dengue virus (DV) is an arthropod-borne virus belongs to the family of Flaviviridae, which is transmitted to humans through the bite of an infected *Aedes* mosquito. There are four serotypes (1 to 4) of the viruses. Once infected, humans become the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes.[2,3] The virus circulates in the blood of an infected person for 2-7 days, at approximately the same time that the person develops a fever. Patients who are already infected with the dengue virus can transmit the infection via Aedes mosquitoes. Dengue virus can be diagnosed serologically by Real-time polymerase chain reaction (RT-PCR) assays, IgM and IgG-ELISA, and the NS1 ELISA-based antigen assay. The clinical spectrum of dengue disease can differ from a mild DF to severe form of the disease, including Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS). Dengue fever (DF) is most commonly an acute febrile illness defined by the presence of fever and two or more of the following, retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leukopenia, mild haemorrhagic manifestation. Anorexia, nausea, abdominal pain, and persistent vomiting may also occur. Dengue haemorrhagic fever (DHF) is characterized by all the features such as fever lasting from 2-7 days, haemorrhagic manifestation or a positive tourniquet test, thrombocytopenia or pleural effusion, or ascites or hypoproteinaemia. Dengue shock syndrome (DSS) has all of criteria for DHF plus circulatory failure as evidenced by rapid and weak pulse and narrow pulse pressure or hypotension and cold, clammy skin and restlessness.[3]

Dengue infection is associated with major changes in haematological profile of the patients. Even though the liver is not the major target organ, pathological findings such as hepatocellular necrosis and inflammatory cell infiltration have been identified in liver biopsy specimens of patients with Dengue and it is reflected by the derangement in liver enzymes.

METHODS

The objective of this study was to assess haematologic profile and the degree of liver injury by measuring the level of the liver enzymes, in Dengue-infected patients. These parameters were compared with the clinical presentations of the patients to evaluate how the degree of liver damage is related to the complications of the disease. This descriptive study was conducted at Dept. of Pathology, Believers church medical college hospital. Serologically confirmed cases of dengue fever from the period June 2016-2017 December were included in the study. Patients with coexistent infections such as Malaria, typhoid and patients with liver diseases, bleeding disorders were excluded from the study. Demographic details, clinical details, laboratory investigations such as total count, differential leukocyte count, platelet count, liver function tests were collected, entered and statistically analysed.

Leukopenia is defined as WBC count below 4,000 cells/cmm, Thrombocytopenia as platelet count less than 1,50,000 cells/cmm. AST and ALT Levels above 40 IU was considered raised. Hypoalbuminemia considered as albumin level below 3.5 g / dl, Hypoglobulinaemia as globulin levels below 2.5 g/dl, bilirubin level above 1.2 mg/dl considered as hyperbilirubinaemia Association of liver enzyme levels (AST and ALT) with severity of Dengue will be tested.

RESULTS

A total of 820 serologically confirmed cases of dengue was included in the study. 800 patients (97.4%) were classical DF case, 7 (1%) were DHF and 13 (1.6%) were DSS. Our study showed a slight female preponderance with a of M:F ratio of 1:1.04. The age of the patient ranged from 4 months to 93 years with a mean age of 43 years. There were 773 adults and 47 paediatric cases. The mean duration of symptoms was 5 + 2 (2 - 11) days. Frequent presenting features were fever, headache, muscle pains, nausea and vomiting, retro-orbital pain and bleeding. Of 820 cases, 751 cases (90.9%) were NS1 antigen positive, and 68 (8.5%) cases were antibody positive and 4 Cases (0.005%) were both antigen and antibody positive. Among the antibody positive cases, 62 were IgM positive, 9 were IgG positive and 5 cases were both IgG and IgM positive. (98.55%) patients were successfully managed and, 1.45% cases expired.

Among the patients which presented with dengue fever, 458 (56%) had leucopoenia, 328 (40%) had normal leukocyte count and 34 patients had leucocytosis (4%). A relative increase in lymphocytes was seen in 290 cases (35%), and absolute lymphocytosis was seen in 97 cases (11%). There were 38 cases (4.6%) with neutrophilia who had clinical features of secondary infection. Thrombocytopenia was seen in 705 (86%) patients, number of cases and degree of thrombocytopenia is as follows.

Platelet Count (lakh/mm^3)	DF	DHF	DSS	Total No. of Cases
0.76-1.5 lakh	252	1	2	255 (32%)
0.20-0.75 lakhs	315	4	4	323 (39%)
< 0.20 lakh	118	3	6	127 (15)

Table 1. Frequency and Grading of Thrombocytopenia in DF, DHF and DSS

The mean platelet count of patients with classical dengue is 0.77 lakhs /mm.^{3} Whereas the mean platelet of people with haemorrhagic manifestation is 0.31 lakhs/mm.^{3} The most common liver function abnormality detected is the

elevation of transaminase level, AST being more than ALT levels. This is followed by hypoalbuminemia and hyperbilirubinemia. Liver transaminase levels were analysed in 720 cases. The reference value of AST and ALT was 40 U/L the grading of liver transaminase elevations is done based on Common Toxicity Criteria for Adverse Events, version 4.03 CTCAE. In this system, the following levels are used to assess severity, with the values expressed as multiples of the upper limit of the normal range (ULN - 40 U/L). Grade 0 represents values <1.5, Grade 1 represents 1.5-3, Grade 2 represents 3-5, Grade 3 represents 5.0-20, and Grade 4 represents >20 times baseline.

Grading	Range of Amino-Transferase	DF	DHF	DSS	Total No. of Cases	% of Cases
0	>1.5 ULN	149	0	0	149	20.6
I	1.5-3 ULN	230	3	1	234	32.5
II	3-5 ULN	148	3	0	151	20.9
III	5-10 ULN	113	1	3	117	16.3
III	10-20 ULN	44	0	4	48	6.7
IV	>20 ULN	17	0	4	21	3

Table 2. Grading of Liver Enzyme Elevation in DF, DHF and DSS

AST was elevated in 91% and ALT elevated in 78% cases. AST appears to be elevated more than ALT in most of the cases. Majority of the cases showed 1.5- to 3-fold increase in transaminase level. The mean AST And ALT level in patients with dengue fever is 184 U/L and 117 U/L whereas the mean AST And ALT level in dengue shock syndrome is 3253 U/Land 1462 U/L showing that there is significant elevation of AST and ALT in DSS than DF ($p<0.0001$).The mean AST and ALT for patients with severe complication leading to death is 3493 U/L and 1573 U/L

AST was elevated more than AST in majority of the patients with AST/ALT ratio more than 1 in 88% cases. Of 820 patients, liver function test such as albumin levels, globulin levels and bilirubin levels were done in 412 patients. Bilirubin levels were elevated in 11% of cases. Serum globulins were decreased in 7% of cases. Serum albumin was low in 38% of cases.

DISCUSSION

Dengue is a mosquito-borne viral infection o which affects up to 100 million people across the tropical world. In recent years, there has been a marked increase in cases of Dengue fever in South-East Asia with the south-east Asia region sharing 52% of global risk for Dengue fever.[4] A total 820 serologically confirmed cases were included in the study. 800 patients (97.4%) were classical DF case, 7 (1%) were DHF and 13 (1.6%) were DSS. 12 out of 13 DSS patients expired with an overall mortality rate of 1.45%. Mortality rate in our study was similar to the study by Mogra G et al (2%),[4] and Sahana et al (2%).[5]

Serological diagnosis of dengue virus infection was done by demonstration of the NS-1 antigen and anti-dengue virus antibodies in the patients' serum. Of 820 cases, 751 cases (90.9%) were NS1 antigen positive, and 68 (8.5%) cases were antibody positive and 4 Cases. This is comparable to study by Chetn Suva et al,[6] and Patel PM.[7] were 86% and 80% cases were antigen positive, 8% and 20% antibody positive.

Our study reports a slightly higher female preponderance with a M:F ratio of 1:1.04 and is in agreement with study conducted in by Daude´E et al´(1:1),[8] and Shekar et al (1.14:1).[9]

Our study showed leukopenia in 56% cases which is in concordance with study by Meena et al (51%),[10] Shams etal (51%),[11] and Tahir et al (56%),[12] and Gitika et al (57%),[13] Other workers like Mehta et al,[14] and Chakravarthi et al,[15] have demonstrated a higher proportion of leucopenic cases (63% and 60%) whereas Rushmavathi et al,[16] and Dutta et al,[17] have reported far lesser cases of leucopoenia in Dengue constituting 33.3% and 30% respectively. Leukopenia with relative increase in lymphocytes was seen in 35% of cases in our study which is similar to the study by Joshi AA et al,[18] and Gitika et al,[13] in which 33% and 40% of cases with leukopenia showed relative increase in lymphocytes. Studies by Christopher J Gregory et al on the utility of WBC count as a marker to differentiate dengue fever from other febrile illnesses, the authors showed leukopenia could be taken up as one of the indicators to separate dengue from other febrile illnesses.[19] Thrombocytopenia in dengue is related to the clinical outcome. Different mechanisms have been hypothesized to explain DENV-associated thrombocytopenia. The most common mechanism explained is the suppression of bone marrow and the peripheral destruction of platelets by antibodies.[20,21] B lymphocytes are the primary circulating cells infected by the dengue virus. The over production of these B cells, along with cytokines like IL–6 trigger an aberrant maturation of plasma cells and atypical lymphocytes leading to the generation of autoantibodies causing platelet destruction and hence thrombocytopenia. The presence of these IgM autoantibodies induces platelet lysis via complement activation and inhibits ADP induced platelet aggregation.[22] Dengue virus can induce apoptotic cell death in early megakaryocytic progenitors. Also direct infection of the bone marrow megakaryocytic precursors and their suppression has been proposed to contribute to thrombocytopenia**.** In addition, DENV infection induces platelet consumption due to disseminated intravascular coagulation (DIC).

Our study showed thrombocytopenia in 86 % patients which is in concordance with the study by Shamsunder Khatroth (83.3 5%).[23] Ageep AK et al (86%),[24] Seema A et al (84%),[25] and Gajera (81%) Vibha V et al (81%).[26]

Thrombocytopenia	Smitha Bhaskar et al.[27]	Khan et al.[28]	Vibha V et al.[26]	Present Study
Mild	34%	35%	34	32%
Moderate	29.4%	26.%	37	39%
Severe	5.8%	1%	10	15%
Percent of Thrombocytopenia	75.29%	71%	81%	86%

Table 3. Comparison of the Degree of Thrombocytopenia with That of Other Studies

Although liver is not the major target organ, changes like centrilobular necrosis, fatty change, Kupffer cells

hyperplasia, acidophilic bodies, and monocytic infiltration of portal tracts have been reported in patients with Dengue fever. Hepatic dysfunction is attributed to a direct viral effect on liver cells or as a consequence of deregulated host immune response, or reflects a complex interaction of these two mechanisms An eventual outcome of hepatocyte infection by DENV is cellular apoptosis. The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response and accelerated endoplasmic reticular stress.[29]

The commonest abnormality detected in our study has been raised transaminase levels. Our study showed raised AST levels in 91% of patients, while raised ALT levels in 78% of patients which is in concordance wit the study by Samantha et al,[30] Kuo et al,[31] Souza et al,[32] Itha et al,[33] Wong et al,[34] Parkash et al,[35] Trung et al,[36] Lee et al,[37] Karoli et al,[38] and Saha et al.[39]

References	Patients	Raised AST	Raised ALT	AST>ALT
Kuo et al	270	93.3%	82.2%	+
Souza et al	1585	63.4%	45%	+
Itha et al	45	96%	96%	
Wong et al	127	90.6%	71.2%	+
Parkash et al	699	95%	86%	+
Trung et al	644	97%	97%	+
Lee et al	690	86%	46%	
Karoli et al	138	92%		+
Saha et al	1226	52%	50%	
Present study	820	91%	78%	+

Table 4. Comparison of AST, ALT Alteration with Those of Other Studies

Transaminase Level	Souza et al[32]	Kulkarni V et al.[40]	Amit Soni et al[41]	Present study
Normal	34.9	14.6	45.6	53.1
1.5-3 UNL	48.5	40.4		
3-10 UNL	14.8	35.8	36.7	37.2
>10 UNL	1.8	9.2	16.4	9.7

Table 5. Comparison of Degree of Transaminitis with Those of Other Studies

Our study showed elevation of AST more than ALT with AST/ALT more than 1 in 88% cases. This preferential elevation of liver enzymes, with AST being significantly higher than ALT was also noted in study done by Rajoo et al,[42] and Itha et al.[33] This pattern is similar to that we see in alcoholic hepatitis but differs from that seen in other viral hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excess release of AST from damaged myocytes during dengue infection. This abnormality may act as an early indicator of dengue and help clinicians to differentiate between these different conditions upon a patient's first presentation.[42,33]

Several studies have been done to find out the association of transaminitis with age, severity, and mortality o patients with dengue infection. The median Aspartate transaminase (AST) and Alanine transaminase (ALT) values have been found to be higher for dengue shock syndrome than for classical dengue fever in our study which is similar to the study conducted by Saha AK.[39] Souza LJ.[32] Wahid SF et al,[43] and Khan et al,[44] This hints at a possible association between increased transaminase levels with increasing disease severity.[44] Wahid et al,[43] and Kuo et al. (1992).[31] also reported higher bleeding episodes in those who had high levels of AST and ALT. Assim et al found that mortality and complications of Dengue fever significantly correlated with liver dysfunction with 100% mortality in patients with severe liver dysfunction. He also found AST was significantly raised in patients with DSS, septicaemia, hepatic and respiratory failure and in patients with encephalopathy. Our study also showed that mortality due to dengue correlated with liver dysfunction as evidenced by very high AST and ALT levels in these patients.

In addition to alteration in transaminase levels, few of the patients showed increase in bilirubin levels as well as decrease in albumin levels. Of 820 patients, liver function test such as albumin levels, globulin levels and bilirubin levels were done in 412 patients. 38% patients showed hypoalbuminemia, 7 % hypoglobulinaemia and 11% had raised bilirubin levels

Alteration in Liver Function	Saha et al[39]	Itha et al[33]	Wong etal [34]	Narasimhan D et al[45]	Present Study
Hypoalbuminemia	12.9%	76%	16.5%	31%	38%
Raised bilirubin	16.9%	30%	13.4%	5%	11%

Table 6. Comparing the Effect of Dengue Infection on Albumin and Bilirubin Levels with Those of Other Studies

CONCLUSIONS

In addition to haematological abnormalities such as leukopenia and thrombocytopenia, dengue virus infection is associated with major derangements of liver function such elevated transaminase levels, hypoalbuminemia and hyperbilirubinemia. The spectrum of hepatic involvement in dengue fever can vary from asymptomatic biochemical involvement to severe acute liver cell injury. Injury to liver cells could result both from direct effect of the virus or due to unregulated immune response of the host; hence, liver function tests are of significance for timely diagnosis and assessment of severity of Dengue fever. It was observed in this study that severity, mortality and complications of acute Dengue fever significantly correlated with liver dysfunction and raised transaminase. Severity of hepatic involvement can be a major contributing factor in morbidity and mortality of Dengue patients and can be used as an early marker to assess the severity of the disease.

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