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Original Research Article

Clinico-Hematological Profile of Dengue Fever during the Monsoon of 2016 in Central Kerala

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ABSTRACT

Background and objective: Dengue is one of the most common mosquito-borne viral infection involving newer areas, newer populations and increasing in magnitude after each epidemic in India. This study is aimed to study the clinico-hematological profile of patients with dengue fever during the monsoon of 2016 in a tertiary care teaching hospital.
Materials and methods: A prospective study conducted in a tertiary care centre in Tiruvalla, Kerala from May 2016 to August 2016.A total of 236 adult patients who were positive for NS1 Antigen were further analyzed for their biochemical, hematological and clinical profiles.
Result: Out of 236, 183(77.5%) were diagnosed as primary dengue and 53 (22.5%) as secondary dengue infection. Common clinical symptoms were fever (100%), generalized body ache (53%), headache (42%), vomiting (22%), and abdominal pain (10%). Thrombocytopenia, leucopoenia and elevated liver enzymes were observed. All patients improved clinically and showed an improvement in their biochemical and hematological parameters. Case fatality among these patients was nil.
Conclusion: Most common form of clinical presentation in our study was primary dengue. Presence of thrombocytopenia and elevated liver enzymes are more indicative of a secondary infection.

Keywords: Dengue, clinical profile, thrombocytopenia

INTRODUCTION

Dengue is one of the most common arboviral infections having significant public health burden in tropical and subtropical countries. According to WHO, almost 50 million people are infected with dengue annually and it is estimated that almost half of the world's population lives in countries having endemicity for dengue infection. [1]

The causative agent of dengue is Dengue Virus which belongs to the genus Flavivirus of the family *Flaviviridae*. There are four serotypes namely DENV-1,DENV-2,DENV-3,DENV-4 and the newly identified DENV-5. [2, 21] The serotypes are closely related but they are antigenically distinct. The infection is transmitted by the bite of female mosquitoes of the genus *Aedes aegypti* and *Aedes albopictus*. Rainy season and post rain season favour the collection of water in various sites which act as a potential source of mosquito breeding. Hence there is increasing frequent outbreaks of dengue especially in regions of endemicity in the monsoon season. [3]

Dengue infection may be subclinical or symptomatic. Symptomatic dengue virus infections can be traditionally grouped into three categories: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). [4] In 2009, WHO proposed a revised and broader clinical classification which is now being adapted; dengue, dengue with warning signs and severe dengue. DF is mainly due to the primary infection by any of the five serotypes, and is generally mild and self-limited, from which recovery is complete. Most common clinical manifestations are fever which may last for 2 - 10 days, headache, retro-orbital pain, myalgia, arthralgia and rash. DHF is due to secondary infection with a serotype different from that which caused primary infection, and is characterized by plasma leakage, thrombocytopenia and haemorrhagic manifestations along with symptoms of primary infection. [1,5] DSS, another form of secondary infection, occurs when fluid and protein leak into the intestinal spaces and results in systemic shock. Both DHF and DSS are serious, often fatal, complications that are marked by problems of capillary permeability and disordered blood clotting. Dengue serotypes vary in their capacity to cause the severity of illness. [6]

After an incubation period of 3 to 15 days (usually 5 to 8 days), classical dengue begins with an abrupt onset of fever (103 to 106°F) accompanied by frontal or retroorbital headache. Flushing of the face and a generalized, transient, macular rash which blanches under pressure may be seen during the first 24 to 48 hours of fever. During 2 to 6 days of fever pronounced anorexia, nausea and vomiting, generalized lymph adenopathy and cutaneous hyperalgesia may develop. In typical cases, fever persists for 4 to 6 days and usually terminates with a crisis. Viremia generally coincides with fever. Defervescence is usually lytic with intense sweating. On the last day of fever or within 24 h, a secondary morbilliform or maculopapular rash lasting 1 to 5 days sometimes appears. Upon appearance of the secondary rash, a second rise in temperature may occur, resulting in a saddleback fever. [7]

The clinical presentation of acute dengue infection is non-specific but 5–10% of patients' progress to severe DHF/DSS, which can result in death if it is not managed appropriately. The major pathophysiological finding of DHF/DSS is plasma extravasation, which differentiates it from DF. DHF/DSS is characterized by high fever, bleeding, thrombocytopenia and haemoconcentration (an increase in the concentration of blood cells because of fluid loss). Approximately 3–4 days after the onset of fever, patients can present with petechiae, rash, epistaxis, and gingival and gastrointestinal bleeding. Pleural effusion and ascites are common. Some patients develop circulatory failure (DSS), presenting with a weak and fast pulse, narrowing of pulse pressure or hypotension, cold and moist skin and altered mental state. [8]

Based on the serological detection of NS1 Antigen and IgM/IgG ratios, dengue cases can also be classified as primary and secondary dengue. [9,27] Serological diagnosis includes NS1 antigen detection, IgM capture ELISA or Reverse Transcriptase (RT)-PCR in acute phase of the disease. Other characteristic laboratory findings of dengue include thrombocytopenia, leucopenia, and elevated liver enzymes. [10] There is no specific therapy for dengue, such as antiviral drugs or vaccination available in India. Only supportive treatments for symptoms, including oral rehydration, administration of intravenous fluids and/or blood transfusion can be employed. In the absence of an effective vaccine or antiviral therapy, early diagnosis and early initiation of aggressive intravenous rehydration therapy, as well as protection against mosquito bites have been shown to be critical in preventing additional outbreaks, and reduce mortality. [11]

This study was aimed to analyze the clinical, biochemical and hematological

parameters of patients during an outbreak of dengue fever during the monsoons of 2016.

MATERIALS AND METHODS

A prospective, cross sectional study was conducted in the department of Microbiology at a tertiary care centre in Central Kerala during the monsoon season of 2016 (from May to August). Ethical clearance was obtained from the Institutional Ethical Committee on 29th October 2015. Adult patients with symptoms consistent of dengue, based on WHO 2009 classification were included in the study. Informed consent was taken and blood was collected for dengue. NS1 Antigen (Panbio Dengue NS1 capture ELISA) dengue IgM and IgG antibody (Panbio Dengue IgM Capture ELISA, Panbio Dengue IgG Capture ELISA) were tested for all samples suspected to be dengue. 236 patients who were tested positive for NS1 dengue antigen were included in the study. Pediatric patients were excluded. Dengue cases were classified as primary dengue and secondary dengue based on the Panbio IgM/IgG ratios. Values<1.2 were considered as secondary dengue and values >1.2 as Primary dengue. [28]

These patients were further analyzed for their biochemical, hematological parameters which included liver enzyme levels, total count, leucocyte and platelet count and clinical variables including fever, headache, generalized body ache, retro orbital pain, abdominal pain, vomiting, loose motion and bleeding manifestations. Presence of co-morbidities was noted. Data was collected in a detailed proforma.

RESULTS

A total of 236 adult patients who were positive for NS1 antigen were included in our study. Out of these, 183(77.5%) were diagnosed as primary dengue and 53 (22.5%) as secondary dengue infection based on IgM/IgG ratio.

The total number of females in our study were 125 (53%) while 111 (47%) were males. Distribution of primary and secondary dengue cases amongst males and females is stated in Table no: 1

Table 1: Distribution of dengue cases among patients (n-236)

Patients	Primary dengue	Secondary dengue
Males (n=111)	90	21
Females (n=125)	93	32
Total	**183**	**53**

Fever was the most common clinical presentation, occurring in all patients at presentation (Table no:2). There was no specific pattern of fever and was usually high grade. Other common clinical symptoms were generalized body ache (53%), headache (42%), vomiting (22%), and abdominal pain (10%). Diarrhea, an atypical symptom was found to be seen in our study population, irrespective of the severity of the infection (10%).

Table 2: Distribution of symptoms in dengue infection

Symptoms	Primary-183 (%)	Secondary- 53 (%)	Total, n -236
Generalized body ache	112 **(61.2)**	24 **(45.2)**	136 **(57.6%)**
Headache	82 **(44.8)**	21**(39.6)**	103 **(43.6%)**
Vomiting	40 **(21.8)**	12 **(22.6)**	52 **(22%)**
Diarrhea*	20 **(10.9)**	5 **(9.4)**	25 **(10.6%)**
Abdominal pain	10 **(5.5)**	4 **(7.5)**	14 **(5.9%)**
Retro-orbital pain	15 **(8.2)**	2 **(3.7)**	17 **(7.2%)**
Rashes	4 **(2.2)**	3 **(5.6)**	7 **(2.9%)**
Bleeding manifestations	-	2 **(3.7)**	2 **(0.8%)**
Co-morbidities			
Type 2 DM*	28	12	40**(20%)**
Hypertension*	38	11	49**(20.7%)**
Bronchial asthma	10	-	10**(4.2%)**
CAD	4	2	6**(2.5%)**

*Statistically analyzed based on Fisher's exact test: showed there is no association between the dengue fever and diarrhea (p value=1.000), there is no significant association between the co-morbidities and the clinical dengue outcome (Type 2 DM p value=0.4196, Hypertension-p value=0.5586).

Abdominal pain, retro-orbital pain, rashes were relatively less frequently observed. Bleeding manifestations were observed only in secondary dengue cases. Thrombocytopenia <1,00,000/mm^3 was seen in 101 (42.7%) patients (table no;3).

Table 3: Distribution of hematological and biochemical parameters in dengue cases

Platelet count	Primary n=**183**	Secondary n=**53**	Total N=**236**
<20000/mm³	2 **(1.09%)**	5 **(9.4%)**	7 **(2.9%)**
20000-50000 /mm³	18 **(9.8%)**	14 **(26.4%)**	32 **(13.6%)**
51000-100000 /mm³	42 **(22.9%)**	20 **(37.7%)**	62 **(26.2%)**
>100000/mm³	121 **(66%)**	14 **(26.4%)**	135 **(57.2%)**
Leucocyte count(< 4000/mm³)	153 **(83.6%)**	12 **(22.6%)**	165 **(70%)**
Elevated Liver enzymes	44 **(24%)**	36 **(67.9%)**	80 **(33.8%)**

DISCUSSION

The first confirmed cases of dengue in India were reported in 1940's, serologically proven cases from Kerala have been reported since late 90's.A rising incidence of dengue fever outbreaks has been reported over the past few years from various states of India which constantly threatens the health care system with respect to associated morbidity and mortality, loss of working hours and health care expenditure.

Kerala state, in a couple of last few decades had undergone an enormous geographical and climatic variation which in turn led to the emergence or resurgence of several vector-borne diseases. [12] In spite of having an excellent primary health care infrastructure as compared to other states, Kerala continues to have regular and increasing dengue outbreaks. The severity and clinical manifestations vary during each outbreak. The widespread awareness programmes and increasing alertness along with availability of newer diagnostic tools for early detection of dengue fever after the early epidemics, have attributed to the early detection of more confirmed cases.

The male-female ratio of 1:1.13 in the present study(table no:1) showed a slight predominance of female population which in accordance with studies by Ashis Kumar Saha *et al*., in a 2012 epidemic in Kolkata in which the ratio was 1:1.08, with slight female preponderance. [13] In other published studies, where there was no significant difference in the proportions by gender. [14] Similarly, one study in Bangladesh, the ratio was 1.5:1 in 1997 epidemic, but in the study of 2000, there was no gender predilection. [15,21] In some studies done in Singapore and India, male to female ratio was 2:1. [16,17]

In the present study, the clinical profile of dengue revealed that fever was the most common presenting symptom. Other symptoms like generalized body ache was more indicative of primary dengue than secondary cases (table no:2).Presence of other symptoms like vomiting, diarrhea, rashes and bleeding manifestations was similar to the study conducted by Ashis Saha *et al.* [13] Study conducted by Sharma et al showed that most common presenting symptom among the dengue cases was fever (100%). [18] Other symptoms reported included body ache (98%), vomiting (28%) diarrhea (12.7%), abdominal pain (10.5%), skin rash (43.1%) and altered sensorium (0.5%). Diarrhea, an atypical symptom has been observed in the present study in 10.6% patients. Although diarrhea was not stated as a warning sign of dengue, the inclusion of diarrhea was justified by the high frequency of the symptom, even though it was not found to be statistically significant. [19] A high incidence of gastrointestinal symptoms like nausea and vomiting were reported in a study from Kerala also and is attributed to hepatomegaly and serosal inflammation. [20]

Thrombocytopenia and leucopenia were the most prominent hematological changes observed in the present study (table no:3). Platelet count below <1,00,000/mm^3 was seen in 101 (42.7%) patients, out of which <50,000/mm^3 was seen in 39 patients. Among these 39 patients, seven patients had

severe thrombocytopenia (<20,000/mm^3) and 32 patients had moderate thrombocytopenia (20,000 to 50,000/mm^3). The remaining 135 patients had platelet count >1,00,000/mm^3. Thrombocytopenia, was also observed in studies by Malathesa et al and Patel et al. [22,23] In the study done by Ratagiri *et al*. and Banerjee *et al*., incidence of thrombocytopenia was 82% and 96% respectively. [24,25] The inhibition of megakaryopoiesis and induction of apoptotic cell death in a subpopulation of early megakaryocytic progenitors may contribute to thrombocytopenia in dengue disease. Dengue virus may also directly interact with and activate platelets causing thrombocytopenia. [26] Two of our patients had bleeding manifestations and their platelet counts were below 30000/mm^3.Surprisingly, the incidence of bleeding in our study manifestation was rare and confined to secondary dengue. The fact that there was no mortality in the study population might be attributed to multiple factors like early detection, aggressive resuscitation including blood and platelet transfusion and adequate nutritional support.

Our study recorded leucopenia (<4000/mm^3) in about 70% patients, whereas, only 21% of patients showed leucopenia in the study by Ratagiri *et al*. [24] Evidence of leucopenia was also demonstrated in the study by Banerjee *et al*, Malathesha *e*t al and in 2012 epidemic study of Ashis Kumar Saha *et al*(80%). [13, 22, 25]

Liver enzymes, both Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were elevated more in secondary dengue 36 (67.9%), than in primary cases. In the present study elevation of AST was more when compared to ALT. In our study, 80 (34%) cases had elevated transaminases which was in concordance with the findings of Samanta J *et al*, where they also observed overall abnormal LFT in 63%. [27] This is because the virus is particularly found in the hepatocytes, Kupffer cells and the endothelium, along with immune complex formation. Hepatocyte infection by DENV is by cellular apoptosis. The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response and accelerated endoplasmic reticular stress. [26] Elevated transaminases levels were more observed in secondary dengue (67.9%) than in primary cases(24%) in the present study. Elevation of AST was more when compared to ALT in the present study and is consistent with the studies conducted by Lee LK *et al*. [29]

All patients were treated symptomatically with optimal intravenous fluids and paracetamol. Ten patients with platelet count of <30,000/mm^3 required platelet transfusion. The duration of stay in the hospital varied with an average of 5 days. Co-existing co morbidities like Type2 Diabetes Mellitus, hypertension was seen in 20% and 20.7% patients respectively. The results were analyzed statistically and observed that there is no statistical significance between the co-morbidities and the clinical outcome. All patients improved symptomatically and had significant improvement of biochemical and hematological parameters. Case fatality in the study group was nil.

CONCLUSION

Our study revealed that the most common form of clinical presentation was primary dengue. Leucopenia was observed more in primary cases. Presence of thrombocytopenia and elevated liver enzymes were more indicative of secondary infection. This study has revealed a varied clinical profile of dengue fever along with the typical symptoms, some atypical symptoms have also been observed. The management of dengue was primarily based on early recognition of symptoms, serological diagnosis, detecting and treating complications promptly and optimal supportive care. Dengue continues to pose a serious challenge to the clinicians, microbiologists and health care workers and more population-based studies and research

are needed to minimize complications, mortality rate and outbreaks.

Conflict of interest: Nil

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