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Original Research Article

Gastrointestinal Manifestations of Dengue Fever and Their Association with Dengue Mortality in a Tertiary Care Hospital Setting in North Kerala

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Abstract

Background: Worldwide incidence of Dengue Fever is on an increasing trend with varying manifestations from mild febrile illness to dengue hemorrhagic fever and shock. Rarely encephalitis, pancreatitis and acute hepatic failure are reported. "Expanded dengue syndrome" is a term used to denote such atypical organ involvement in Dengue among which gastrointestinal system involvement is relatively common.

Aim: To estimate the incidence of gastrointestinal manifestations in dengue infected individuals and their association with lab investigations and mortality.

Materials: A prospective, observational study was conducted in 500 patients with Dengue fever, confirmed by NS1 antigen and /or IgM antibody tests. A semi-structured questionnaire-based data collection was used.

Results: Among the 500 patients with confirmed dengue fever 50% had liver involvement (46% had SGOT > 100U/l and 34% had SGPT >100U/l). 13% an associated pancreatitis was observed. Significant factors contributing to the mortality were Age, presence of Ascites, SGOT>500 U/l, SGPT> 500 U/l and systolic BP < 100 in critically ill patients.

Conclusions: Despite the small sample size, the study inferred those gastrointestinal manifestations were relatively common in dengue. Presence of high liver enzymes and pancreatic enzymes could be used to triage patients requiring intensive care to reduce mortality.

Keywords: Dengue, Gastrointestinal Manifestations, Liver Enzymes, Pancreas, Mortality, Risk Factors.

Background

Dengue, a mosquito-borne viral disease is a major global public health challenge in the tropic and subtropic nations. Internationally, this disease is considered as the most important arboviral disease, and it imposes significant socioeconomic and disease burden in underdeveloped countries (WHO, 2012–2020. Geneva, 2012-2020) [1]. More than 50% of the world's population currently lived in areas where people are at risk of developing the disease (Gubler, 2011) [2]. It is mainly endemic to the tropical and subtropical countries of South and Southeast Asia, the Caribbean, Central & South America and Africa. Dengue fever has been the most rapidly spreading mosquito-borne viral disease among human beings and has witnessed a 30-fold upsurge worldwide between 1960 and 2010 Increasing trend in the rate of population growth, global warming, unplanned urbanization, inefficient mosquito control, frequent air travel, and lack of health care facilities have been some of the major contributors (Hasan *et al.*, 2016) [3]. Dengue is caused by one of the four serotypes of DEN virus (DENV-1 to DENV-4) belonging to the family *Flaviviridae*. (Malaiyan, *et al.*, 2020) [4] In India, multiple virus serotypes exist, and cyclical epidemics are quite frequent (Sathish *et al.*, 2020) [5]. Manifestations of dengue may range from a mild symptomatic disease to severe complications including dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Rarely, complications such as acute myocarditis, acute hepatic failure, acalculous cholecystitis, and acute pancreatitis are also reported (Mcfarlane, *et al.*, 2013) [6] (Khor *et al.*, 2006) [7]. Classical clinical symptoms of dengue fever include fever that lasts for a period of 2-7 days with associated symptoms including headache, pain in retro-orbital area, myalgia, arthralgia, backache and rash [8]. 'Expanded dengue syndrome' (EDS) is a relatively new category to be included in the WHO [8] classification of dengue infection. EDS includes atypical presentations of dengue, involving neurological, hepatic, renal, cardiac and other isolated organ involvement. Among these, gastrointestinal manifestations, although common in dengue fever, are most often missed due to lack of awareness (Medina, *et al.*, 2011) [9] (Prashanth V [10]. & Nimmagadda S.S. etal 2014) [11]. Early recognition and proper management by an experienced team can save lives - decreasing mortality rates from >20% to less than 1% (WHO, 2017) [1]. This study aimed to estimate the incidence of gastrointestinal manifestations and liver involvement in patients admitted with confirmed Dengue fever in Government Medical College, Calicut which is one of the major tertiary care centres in North Kerala. Further, the study evaluated the profile of laboratory and radiological parameters in association with mortality in the critically ill Dengue infected patients.

Methods

At a tertiary care hospital over a period of 3 years from July 2017 to July 2020 in the outpatient department (OPD) or casualty of Department of Internal Medicine, 500 patients with Dengue fever and positive NS1and /or IgM Dengue positivity were studied for their gastrointestinal manifestations; biochemical and radiological changes and the role of these factors on the mortality were analyzed. An Institutional ethics committee approval was obtained for the study and a written informed consent and pre-tested semi structured questionnaire proforma was

used for the 500 patients admitted during the study period. The age and gender, gastro-intestinal manifestations such as vomiting, diarrhoea, abdominal pain, and ascites, liver and spleen enlargement were recorded. Laboratory parameters such as haematocrit, platelet count, hepatic transaminase (SGOT- Serum glutamic oxaloacetic transaminase, SGPT- Serum glutamic pyruvic transaminase), serum bilirubin, albumin, and amylase and lipase values were estimated. CT abdomen and Ultrasonography were done to detect atypical manifestations like pancreatitis, cholecystitis, gall bladder oedema, appendicitis and GI bleed in selected cases. The laboratory test values and radiological findings of patients who expired were compared with values of the patients discharged to learn their significance.

Sample size: Based on the previous study done in Kollam in Kerala (Daniel *et al*., 2005), the prevalence of Diarrhoea in confirmed dengue was 15.2%. Considering 15% prevalence for diarrhoea and assuming an absolute precision of 3.5 %, the sample size was calculated using the formula: $4pq/d^2$ was $4x15x85/ (3.5)^2 = 417$. Hence 500 patients with positive NS1 and / or IgM Dengue were randomly selected and enrolled in the study.

Statistical analysis: The data was analyzed using standard statistical methods like, mean, standard deviation, percentage and factors associated with dengue mortality were found using Odds ratio with 95% Confidence interval. To adjust for confounders, multivariate analysis was done.

Results

The demographic data of the 500 subjects in the study was analyzed and found that 389/500 (78.2%) were aged between 21 to 60 years able 1 provides the demographic profile of the study population. 48 (09.8%) subjects were aged 12 to 20 years. Out of 500 subjects, 326 (65.2%) were males and 174 (34.8%) were females with a male to female ratio of 1.87:1. 98.4% of dengue cases were cured and discharged from hospital, whereas 1.6% (N=8) succumbed to disease. The most common gastrointestinal manifestation was vomiting (36%), [Table 1].

Table 1: Shows the demographic details and symptoms observed in the study (n-500).

Parameters	Number	Percentage
Age (years)		
12-20	48	09.6
21-40	207	41.4
41-60	182	36.4
61-90	61	12.2
Gender		
Male	326	65.2
Female	174	34.8
Signs and symptoms		
Vomiting	180	36.0
Diarrhea	48	09.6
Abdominal pain	106	21.2
Ascites	15	03.0

Among the 500 subjects with confirmed Dengue fever in this study 243 (48.6%) had raised SGOT enzyme levels of above 100 U/L in their serum and raised SGPT levels were observed in 178 (35.6%) of them. [Table 2] Serum lipase more than 300 U/L was observed in 68 (13.6%0 subjects and 26 (5.2%) had Serum amylase >300 U/L which was suggestive of pancreatitis [Table 2].

Table 2: Shows the biochemical test values in the subjects (n-500)

Liver function profile	Number	Percentage
SGOT in U/L		
<30	057	11.4
31-100	200	40.0
101-300	151	30.2
301-400	056	11.2
401-500	026	05.2
501-1000	010	02.0
SGPT (in U/L)		
<30	055	11.0
31-100	267	53.4
101-300	143	28.6
301-400	019	03.8
401-500	006	01.2
501-1000	010	02.0
Total Bilirubin mg/dL		
<1	420	84.0
1-1.5	62	12.4
>1.5	18	03.6
Albumin g/dL		
0-2	23	04.6
2.5-3.5	320	67.0
>3.5	156	42.8
Serum Amylase U/L		
01-30	162	32.4
31-100	214	42.8
101-300	98	19.6
301-500	18	18
501-1000	08	08
Serum Lipase		
<30	141	28.2
31-100	188	37.6
101-300	103	20.6
301-400	39	07.8
401-500	29	05.8

(SGOT- Serum Glutamic-oxaloacetic Transaminase; SGPT - Serum Glutamic Pyruvic transaminase)

Ultrasound examination of the abdomen showed normal findings among 448/500 (89.6%) patients. Ascites was noted in 30 (06%), Gall Bladder oedema was noted in 08 (01.6%), pancreatitis was noted in 07 (01.4%), Cholelithiasis was noted in 04 (0.8%) and appendicitis in 01 (0.2%) patients. The Mean Hematocrit value noted was 42.46.

The unadjusted Odds Ratio (OR) revealed age ate more than 60 years. Presence of ascites during admission, elevated SGOT and SGPT levels above 500 U/L, elevated serum amylase greater than 500 U/L were noted as significant ($p<0.05$) risk factors contributing to the mortality in Dengue fever (Table 3).

Table 3: Risk Factors associate with mortality rate in Dengue Fever in the study (n-500)

Variables	Frequency in expired population (%)	Frequency distribution in cured population (%)	†P value	*Crude OR (95% CI)
Age >60yrs	4 (50%)	57 (11.6%)	0.001	7.6 (1.8-31.35)
Male gender	6 (75%)	2 (25%)	0.557	1.6 (0.322-8.07)
Presence of Abdominal pain	2 (25%)	104 (21.1%)	0.67	1. 2 (0.24 - 6.2)
H/o Alcohol intake	1 (12.5%)	31(6.3%)	0.477	2.12 (0.25 - 17.81)
Systolic BP<100	2 (25%)	55 (11.2%)	0.22	2.6 (0.52-13.1)
Presence of ascites	2 (25%)	13 (2.6%)	0.0001	12.2 (2.26-66.7)
Platelet count <20,000	3 (37.5%)	179 (36.4%)	0.6	1.04 (0.24-4.44.2)
SGOT >500	2 (25%)	24 (4.9%)	0.011	6.5 (1.3 - 33.9)
SGPT >500	2 (25%)	4 (0.8%)	0.0001	40.6 (6.2 - 266.1)
SERUM AMYLASE >100	4 (50%)	120 (24.4%)	0.09	3.1(0.7 - 12.5)
SERUM Lipase >500	1 (12.5%)	28 (5.7%)	0.41	2.37 (0.28 - 19.9)
SERUM Albumin <2.5	1 (12.5%)	22 (4.5%	0.2	3.05 (0.36 - 25.9)

(*Unadjusted OR, † P value from Pearson's Chi-square test/Fisher's exact test when appropriate CI = Confidence interval, OR = Odds ratio)

An additional logistic regression analysis suggested only three variables Age >60 years Presence of Ascites and Serum amylase > 500U as significant risk factors for mortality in dengue (Table 4 The model showed a Nagelkerke R square of 0.31. The Omnibus tests of Model coefficients gave a $\chi 2 = 23.73$ (df = 3, P < 0.001).

Table 4: Logistic Regression for factors associated with risk of mortality in Dengue

Variables	Adjusted OR*	95% CI	P value
Age >60yrs	8.948	2.03-39.51	0.004
Presence of ascites	13.45	2.22-81.5	0.005
Systolic BP < 100	4.608	1.7-28.1	0.05

(*OR = Odds ratio got from logistic regression. CI = Confidence interval)

Discussion

The present study demonstrated a relatively much common prevalence of gastrointestinal manifestations in dengue fever, especially among critically ill dengue patients. Age above 60 years, presence of ascites and elevated serum amylase levels are significant risk factors associates with mortality burden among the study population. Our study population majorly included the young patients, consistent with previous observation which showed mean age of dengue infected patients in the range of 27 to 33 years (Prashanth V10. & Nimmagadda S.S *et al* 2014) [11], (Kularatne, *et al*., 2018) [12]. Gastrointestinal manifestations although frequently missed are relatively common among patients with dengue. Various gastrointestinal manifestations frequently encountered were vomiting, diarrhoea and abdominal pain. A previous study has also observed nausea (43.3%), vomiting (40.2%), pain abdomen (41.3%) as more common GI symptoms

(Nimmagadda, 2014) [11]. A study by B Jayasundara [13] showed elevation of transaminases between 30-50% which is similar to our finding (Jayasundara *et al*., 2017) [13]. Elevated serum amylase and serum lipase >500 was also depicted in study done by V. Jain *et al* (Jain *et al*., 2014) [14]. Ascites was also an important gastrointestinal manifestation. In this study among those who expired, there were significantly higher proportions of patients in the age group of over 60 years, with ascites and with elevated liver enzymes. Previous studies have reported elevated hepatic transaminase >500 IU/L (Medagama et al., 2020) [15] and SGPT >300 IU/L (Almas *et al*., 2010) [16] (Chowdhury *et al*., 2013) [17] as significant independent predictors or mortality among dengue patients. Significance of age as a risk factor in dengue fever mortality was supported by a similar study by Egger *et al* and Paixao (Egger & Coleman, 2007) [18] (Paixão, *et al*., 2015) [19]. This study has limitations as it was a small sample size, especially in the mortality group. However, it lends scope to further explore using large scale observational studies.

Conclusion

Gastrointestinal manifestations are relatively much common in Dengue fever and there has been a lack of awareness. While vomiting, abdominal pain and diarrhoea are the common GI symptoms, atypical manifestation including pancreatitis, gall bladder oedema, appendicitis and internal bleed were less common. Associated high levels of liver enzymes and pancreatic enzymes could be used to triage patients requiring intensive care to prevent mortality.

Conflict of Interest Statement:

The authors declare that they have no conflict of interests.

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