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Gastrointestinal manifestations in patients with dengue fever: an observational study

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Abstract

Background: Dengue fever is an arthropod borne viral disease with multisystem involvement and varied clinical presentation. This research work aimed at studying the spectrum of gastrointestinal (GI) manifestations in patients with dengue fever.

Method: This was a prospective observational study in which hospitalized adult patients with dengue fever in Chitwan Medical College, Nepal were consecutively enrolled from August to December 2023. Ethical approval was obtained. Clinical presentation, laboratory findings and outcomes were recorded. Gastrointestinal manifestations included symptoms (pertaining to GI tract, hepatobiliary and pancreas), laboratory and imaging findings. Warning sign and features predictive of severe form of dengue were analyzed. Data analysis was done using SPSS version 20.

Result: Out of 119 dengue patients, females were 63(53%), 44(37%) had warning signs and 10(8.4%) had severe dengue. At least one gastrointestinal and/or hepatic manifestation was present in 110(92.4%) and at least one gastrointestinal symptom in 92(77.3%) patients. The most common gastrointestinal manifestations were nausea (68.9%), vomiting (56.3%), pain abdomen (25.2%), diarrhea (15.1%), and melena (<1%). Hypertransaminasemia (79.8%) was the most common laboratory abnormalities followed by jaundice (5.0%), hepatomegaly (5%), and splenomegaly (5%). There was one mortality. Multivariate analysis showed vomiting and pain abdomen were two features that were predictive of severe form of dengue.

Conclusion: Gastrointestinal manifestations were common (92.4% of 119) in dengue fever, and in this study abdomen pain and vomiting were predictive of severe dengue.

Keywords: Dengue Fever, Gastrointestinal Manifestations, Severe dengue, Warning signs

How to cite

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Introduction

Dengue fever is caused by infection with one of four serovars of dengue viruses (DENV). It is an arthropod –borne disease transmitted by bites of Aedes Mosquito.[1] The clinical spectrum of the disease ranges from mild febrile illness (dengue fever without warning signs) to severe dengue with multiple organ-systems involvement.[2,3]

The clinical disease may manifest in 3 phases- febrile phase, critical phase and a recovery phase; the last two being seen only in cases of dengue with warning signs and severe dengue but not in dengue fever without warning signs.[2]

Diagnosis of dengue fever is suspected in any febrile patient with typical manifestations like headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting, rashes, hemorrhagic manifestations, especially when there is relevant epidemiological exposure. Being a multisystem disease, dengue fever also involves different components of the gastrointestinal (GI) tract and has varied GI manifestations. Several atypical GI manifestations have been reported in patients with dengue fever. They include hepatitis, acalculous cholecystitis, acute pancreatitis, diarrhea, ascites, upper GI bleeding and even fulminant hepatic failure.[4]

Though dengue is common in Nepal, there is scarcity of data regarding GI and hepatic manifestations and effect of these symptoms on the disease severity. The aim of this research was to analyze the GI manifestations and related laboratory parameters in patients with dengue fever. It also aimed to analyze association between GI manifestations and severity of dengue fever.

Method

This was a prospective single center observational study conducted between August to December 2023 in the Department of Internal Medicine, Division of Medical Gastroenterology, Chitwan Medical College, Bharatpur, Chitwan, Nepal. All the consecutive patients diagnosed with dengue according to standard criteria aged ≥18 years were included. The study was approved by the institute's review committee (approval number 080/081-061). A diagnosis of dengue was achieved by either rapid diagnostic test or enzyme link immunoassay (ELISA) for dengue non-structural protein-1 (NS1) antigen or IgM antibody against dengue in addition to the symptoms. The exclusion criteria included patients with other concomitant infections, pregnancy and patients with preexisting GI, liver or pancreatic disease. The severity of Dengue infection was graded according to the World Health Organization (WHO) Dengue guidelines.[2] Clinical presentation, physical examination findings, laboratory data and outcomes were recorded. Radiological investigations were guided by clinical presentation and included chest X-rays, ultrasonography and computed tomography scans.

Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 20. Categorical variables were expressed as n(%), continuous variables with normal distribution with mean ±SD, and continuous variables with skewed presentation with median (range).

Associations between the categorical variables were determined using the Chi-square test or the Fisher's exact tests wherever applicable. Univariate and multivariate regression methods were applied to assess the predictability of disease severity through the GI manifestations.

A two tailed $p<0.05$ was considered as significant. However, those variables which were significantly associated at $p<0.25$ in bivariate analysis was fitted into Logistic regression model based on simulation study, Table 5.

Result

Among the 119 patients included in the study, 92(77.3%) were positive for NS1, 19(15.9%) had IgM serology positivity, 6(5.0%) were positive for both NS1 and IgM, while 2(1.6%) had IgM and IgG serology positivity.

Sixty-three (53%) patients were female. The mean age of the entire cohort was 34.2 ± 13.8 years. Dengue without warning signs, dengue with warning signs, and severe dengue was seen

in 65(54.6%), 44(36.9%), and 10(8.4%) patients respectively, Table 1.

The GI manifestations

GI and hepatic manifestations were common among the patients. At least one GI and/ or hepatic manifestation was seen in 110(92.4%) of patients. Ninety-two (77.3%) patients had at least one GI symptom. Seventy-Eight (65.5%) patients had both GI and hepatic involvement, Table 2. Nausea was the most common symptom reported in 82(68.9%) patients, and melena the least common in 1(0.8%). The presence of ascites [12(10.1%)] was the most common GI abnormality on imaging and pancreatitis the least common in 1(0.8%), Table 1 and 2.

Table 1. Baseline characteristics of the patients according to disease severity (n=119)

Clinicodemographic features of dengue	Without warning signs 65(54.6%)	With warning signs 44(37%)	Severe dengue 10(8.4%)
Demographics			
Age in years, mean ± SD	33.9 ± 12.3	34.9±15.9	33.1 ± 13.9
Male sex, n(%)	35(53.8)	18(40.9)	3(30)
Comorbidities, n(%)			
HTN	4(6.2)	1(2.3)	0
DM	0	2(4.5)	0
Hypothyroidism	4(6.2)	0	0
GI manifestations, n(%)			
Nausea	35(53.8)	38(86.4)	9(90)
Vomiting	21(32.3)	36(81.8)	10(100)
Pain Abdomen	5(7.7)	19(43.2)	5(50)
Diarrhea	9(13.8)	8(18.2)	1(10)
Melena	0	0	1(10)
Ascites	1(1.5)	9(20.5)	2(20)
Jaundice	0	2(4.5)	4(40)
Hypertransaminasemia	49(75.4)	39(88.6)	8(80)
Laboratory findings, mean±SD			
Hemoglobin-g/dl	12.33±1.79	12.16±1.72	12.26±3.35
Hematocrit-%	36.54±5.03	35.71±5.21	36.23±10.35
Total count- /mm^3	4606.92±3082.47	4923.86±3346.05	7260.00±4408.08
Platelets -/mm^3	135123.08±68973.62	89659.09±44919.02	92200.00±58874.25
Urea-mg/dl	21.79±7.25	22.71±8.56	44.35±33.30
Creatinine-mg/dl	0.90±0.25	0.84±0.25	1.38±1.20
Sodium-mEq/L	136.74±2.63	134.72±19.03	138.80±3.68
Potassium mEq/L	3.96±0.35	3.99±0.37	4.03±0.54

HTN: Hypertension, DM: Diabetes Mellitus

Table 2. GI and hepato-pancreatico-biliary manifestation among the patients (n=119)

GI/hepato-biliary manifestation	n(%)
Nausea	82(68.9)
Vomiting	67(56.3)
Pain abdomen	30(25.2)
Diarrhea	18(15.1)
Melena	1(0.8)
Ascites	12(10.1)
Jaundice	6(5.0)
Hepatomegaly	5(4.2)
Splenomegaly	5(4.2)
Hypertransaminasemia	95(79.8)
Pancreatitis	1(0.8)
Fulminant Hepatic Failure	1(0.8)

Hypertransaminasemia in 95(79.8%) patients was the most common laboratory abnormality. Aspartate transaminase levels as high as 6456 U/L and Alanine transaminase levels as high as 3252U/L were also observed. AST and ALT levels exceeding 1000U/L were found in 2.5% and 1.7% of patients respectively. Elevated levels of Alkaline Phosphatase (ALP) were observed in 21% of the patients. The highest recorded ALP level was 987U/L. Hyperbilirubinemia was seen in 26.9% of patients. The highest level of bilirubin seen among these was 12mg/dL. Cholestatic, mixed and hepatocellular patterns of liver injury were seen in 59(49.6%), 39(32.8%), and 21(17.6%) patients respectively, Table 3.

Other manifestations and outcomes

Apart from fever in 119(100%), myalgia 84(70.6%) and headache 76(63.9) most common. Retro-orbital pain 49(41%), rashes 9(7.6) and polyarthralgia 7(6%), were other non-GI manifestations.

Eleven (9.2%) patients developed pleural effusion, 5(4.2%) acute kidney injury (AKI), and 2(1.7%) patients each had acute respiratory distress syndrome (ARDS), and encephalopathy and peripheral edema. The median days of hospital stay in patients without warning signs, with warning signs and severe dengue were 3, 3.5 and 6 days respectively. There was one mortality among patients with severe disease.

The system wise analysis revealed that the most patients had some sort of hematological abnormality. The GI and hepatological involvement were second most involved system, Figure 1. Univariate and multivariate analysis of GI manifestations predictive of more severe form of disease. Among the various GI manifestations, vomiting (OR 7.37, 95% CI 1.96-27.6.6, p=0.003) and pain abdomen (OR 4.5, 95% CI 1.4-14.8, p=0.013) were found to be predictive of a more severe form of disease on multivariate analysis. Table 4 and Table 5. Six (5%) patients had some form of bleeding manifestation, Figure 2.

Table 3. Liver biochemical parameters of patient dengue patients (n=119)

Parameter	n(%)
Bilirubin(mg/dl), min 0.23, max 12.0	
<1	87(73)
1-2	22(19)
2-3	4(3)
>3	6(5)
AST(IU/L), min 13, max 6456	
Normal	28(24)
1-2 times UNL	27(23)
2-3 times ULN	16(13)
>3X ULN	48(40)
>1000	3(2.5)
ALT(IU/L), min 10, max 3252	
Normal	37(31)
1-2 times UNL	27(23)
2-3times ULN	19(16)
>3X ULN	36(30)
>1000	2(1)
ALP(IU/L), min 40, max 987	
Normal	94(79)
1-2 times UNL	17(14.3)
2-3times ULN	6(5)
>3X ULN	2(1.7)
R Factor, min 0.48, max 58.5	
<2	59(49.6)
2-5	39(32.8)
>5	21(17.6)

AST: Aspartate Transaminase, ALT: Alanine Transaminase, ALP: Alkaline Phosphatase

Table 4. Univariate analysis of GI manifestations associated with severe form of dengue (n=119)

GI manifestation	Odd's ratio	p-value	95% CI
Nausea	5.476	<0.001	2.158-13.895
Vomiting	11.250	<0.001	4.530-27.939
Pain abdomen	8.276	<0.001	3.049-22.460
Diarrhea	1.295	0.613	0.475-3.536
Ascites	7.442	0.012	1.554-35.649
Jaundice	6.771	0.085	0.766-59.849
Hepatomegaly	0.824	0.835	0.133-5.118
Splenomegaly	5.306	0.141	0.575-48.975
Hypertransaminasemia	2.280	0.095	0.866-6.001

Table 5. Multivariate analysis of GI manifestations associated with severe form of dengue (n=119)

GI manifestation	Odd's ratio	p-value	95% CI
Nausea	0.996	0.995	0.235-4.212
Vomiting	7.365	0.003	1.964-27.618
Pain abdomen	4.487	0.013	1.364-14.765
Ascites	3.781	0.157	0.598-23.902
Jaundice	2.083	0.567	0.168-25.759
Hepatomegaly	0.668	0.756	0.053-8.449
Splenomegaly	4.551	0.257	0.331-62.555
Hypertransaminasemia	1.242	0.726	0.369-4.184

Simulation study- Purposeful selection of variables in logistic regression

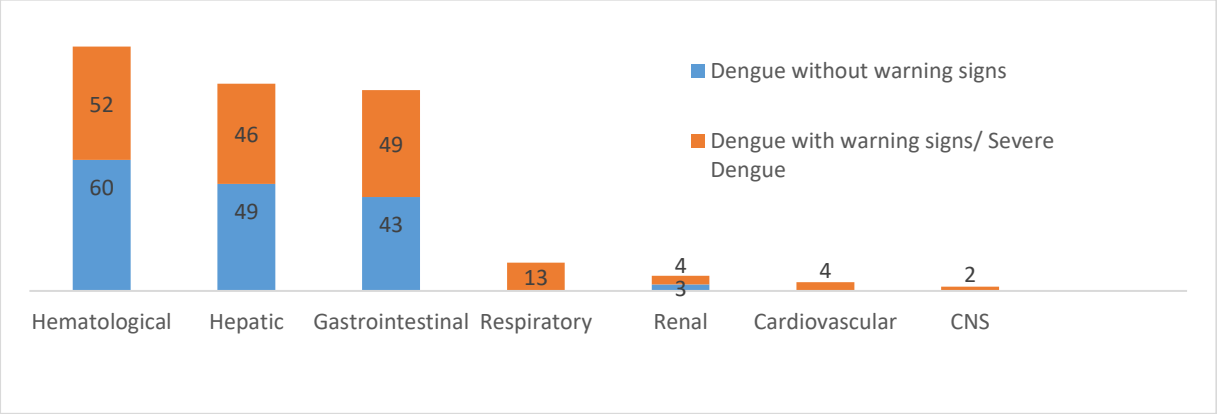

Figure 1. Various system involvement among dengue patients (n=119)

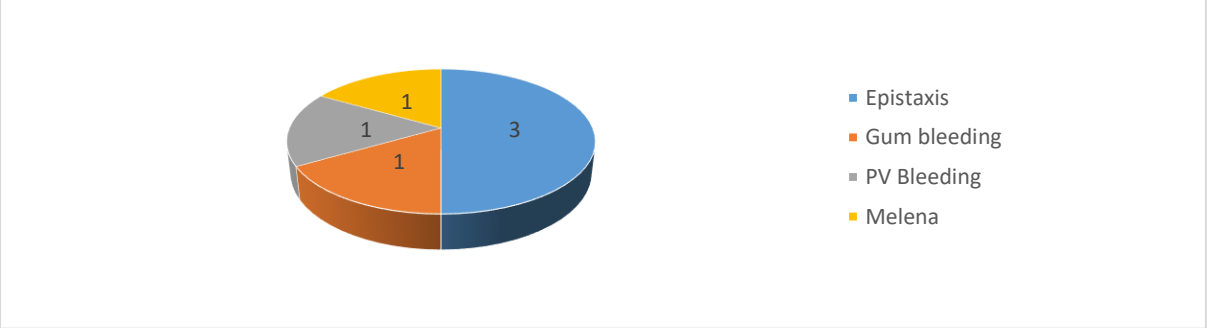

Figure 2. Various bleeding manifestations among dengue patients (n=119)

Discussion

In this prospective observational study examining the GI manifestations in the patients admitted with dengue fever, we found that GI manifestations are common, affecting almost 92% patients. The most common manifestations were nausea, vomiting, pain abdomen, diarrhea and jaundice. The alteration in liver panel tests was seen in almost 80% of patients. The most common radiological abnormalities were ascites, hepatomegaly and splenomegaly. The current study also demonstrates that the presence of pain and vomiting predicts the development of severe dengue.

A high incidence of GI manifestations has been reported from previous observational studies, too.[10-12] This high incidence of liver involvement in our patients is in line with previously reported rates with studies suggesting 80-90 % cases with hypertransaminasemia.[13,14] These findings do suggest that GI and hepatic involvement is common in patients with dengue. This could be explained on the basis of direct hepatotoxic effect of dengue virus and deranged host immune response to the infection. It is found that hepatocytes and Kupffer cells are the prime targets of dengue virus.[15] Apart from luminal and hepatic involvement, previous studies have also reported other manifestations like acalculous cholecystitis, pancreatitis, appendicitis and fulminant hepatic failure.[5-9] The incidence of such conditions in our patients were low, probably because the proportion of severe cases in our study population was relatively smaller and these studies were mostly case series and case reports. Another factor affecting the disease manifestation could be the sero-variety of the virus which was not determined in our patients.[16]

Our study also found that of all symptoms of GI involvement, the presence of vomiting and pain abdomen were the only predictors of more severe form of disease. This is in line with the WHO classification of severe dengue where presence of pain abdomen is considered as warning sign .[2] Pain abdomen was also found to be predictive of severe disease and need for ICU care in patients with dengue in previous studies.[17, 18]

Our study had a smaller number of severe dengue cases which could affect many outcomes of this study. However, small number of severe diseases is consistent with previous study from South India.[19]

The limitations of our study include- relatively smaller sample size, smaller proportion of patients with severe disease, inclusion of only adult patient population, non-determination of dengue serovars which could affect the clinical presentation of the disease. This study findings could be helpful in predicting a severe disease in advance and also in early recognition of the disease related complications.

Conclusion

GI and hepatic manifestations are common occurrence in patients with dengue fever and presence of vomiting and pain abdomen are predictive of disease severity.

Author contribution

Concept and design- PN, BM, RKY, SS, RM, MKR; Literature review- PN, RKY, LS, SS, MKR; Data collection- PN, RKY, LS, SS, RM, MKR; Data analysis- PN, BM, RKY, MKR; Draft- PN, BM, RKY, LS; Accountability- All authors have read and agreed to the final version of the manuscript.

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Conflict of interest

None

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Supplementary material

The data and supplementary material that support the findings of this study are available from the corresponding author upon reasonable request.

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