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Original Research Article

A study on Hematological parameters in dengue virus-infected patients at Tertiary care Teaching Hospital

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Abstract

Background: Dengue virus infection (DI) is an important health problem in many Southeast Asian countries. In recent years, several epidemics of DI have been reported from India. Liver involvement is known to occur in children with DI. The degree of liver dysfunction in children with DI varies from mild injury with elevation of transaminase activity to severe injury with jaundice; a few patients have presented with a clinical illness resembling liver failure. The severity of liver dysfunction varies according to the type of clinical presentation of DI, and is more common in patients with complicated dengue. ***Materials and methods:*** This is a prospective, cross-sectional, hospital-based study was carried out in the Department of Pathology at Tertiary Care Teaching Hospital over a period of 1 year. Clinical examinations were performed by a physician on each study participant. Demographic variables, as it has been published in previous work, and clinical profiles of study participants were collected by nurses using the structured questionnaire. The diagnosis of dengue was made based on positive enzyme-linked immunosorbent assay result for specific IgM antibody for dengue in serum. ***Result:*** When compared to dengue-negative cases, dengue-positive cases had thrombocytopenia, leucopenia, erythrocytosis, high hemoconcentration, low mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). However, binary logistic regression predicted platelet count, total leucocytecount, MCH, MCHC, neutrophil count and lymphocytecountas significant predictors of dengue positivity. ***Conclusion:*** In conclusion, liver injury is nearly universal in adult patients with DI. Though liver involvement is asymptomatic in a large majority, in some patients it leads to clinical manifestations of liver disease and may occasionally lead to acute liver failure and death. Care must be taken to not make a mistaken diagnosis of viral hepatitis. Further studies are needed to define the mechanisms of liver injury due to this infection.

Keywords: Dengue Hematological parameters Thrombocytopenia Nepal.

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INTRODUCTION

Dengue fever is a viral infection transmitted by mosquitoes, primarily the Aedes aegypti mosquito. It is prevalent in tropical and subtropical regions worldwide and can lead to severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are characterized by severe bleeding and plasma leakage. [1]

Dengue virus infection (DI) is an important health problem in many Southeast Asian countries. In recent years, several epidemics of DI have been reported from India. [2] Liver involvement is known to occur in children with DI. [3] The degree of liver dysfunction in children with DI varies from mild injury with elevation of transaminase activity to severe injury with jaundice; a few patients have presented with a clinical illness resembling liver failure. [4] The severity of liver dysfunction varies according to the type of clinical presentation of DI, and is more common in patients with complicated dengue. [5]

Hematological parameters play a crucial role in the diagnosis and management of dengue fever. Here are some key hematological parameters commonly observed in patients with dengue fever. Monitoring these hematological parameters is essential for diagnosing dengue fever and assessing disease severity. [6] Timely intervention, including fluid management and supportive care, is crucial, especially in patients with severe dengue manifestations. Close monitoring of hematological parameters helps healthcare providers in the management and prognosis of patients with dengue fever. [7]

Most of the available data on liver involvement in DI are from children, and data from adults are scare. We therefore studied the profile of liver involvement among a group of predominantly adult patients affected during a recent outbreak of DI in India and compared the severity of such involvement among patients with DI of varying severity.

MATERIALS AND METHODS

This is a prospective, cross-sectional, hospital-based study was carried out in the Department of Pathology at Tertiary Care Teaching Hospital over a period of 1 year.

Inclusion criteria

Febrile patients who were presumed for dengue infection based on 2009 WHO criteria and serologically confirmed with dengue specific IgM antibody. The febrile patient is referred to one whose axillary temperature is ≥ 38 oC.

Exclusion criteria

Cases confirmed as malaria, Kala-azar, typhoid fever, and any other confirmed chronic diseases were excluded in the study.

Clinical examinations were performed by a physician on each study participant. Demographic variables, as it has been published in previous work, and clinical profiles of study participants were collected by nurses using the structured questionnaire. The diagnosis of dengue was made based on positive enzyme-linked immunosorbent (ELISA; manufactured by EUROIMMUN diagnostics) assay result for specific IgM antibody for dengue in serum. All the routine investigations such as hematological determination like total leukocyte count (TLC), differential leukocyte count, platelet count; hemoglobin (Hgb) and hematocrit (Hct) were determined by the automated blood analyzer. Thick and thin blood smear for malaria parasite, biochemical tests; AST and ALT for liver function tests, creatinine, and BUN for renal function tests and total protein were done by the automated biochemistry analyzer (Vegasys). The cutoff values of each test results were considered based on reference ranges used by the laboratory. Furthermore, medical charts of all dengue specific IgM positive cases were reviewed for the collection of other information (i.e. Kala-azar, typhoid fever, and any other confirmed chronic cases).

RESULT

3.1. Characteristics and demographics of dengue-positive cases

The overall dengue-positive cases were 90. Among them, 55.6% (n=50) were single positive, 33.3% (n=30) were dual positive, and triple positive were found to be 11.1% (n=10) (Table1). The median age of dengue-positive participants was 30 years (Q3-Q1 = 44 years – 22 years). Among 788 dengue-positive subjects, 51.8% (n= 408) were male vs. 48.2% (n= 380) female. Furthermore, the age group 20-29 years was found to have higher positive cases, followed by 30-39 years (Figure 1). Mann- Whitney test revealed that the age in the dengue-positive group (median = 32 years) was significantly higher than in the denguenegative group (median = 30 years); p=0.005 (Table 2).

3.2. Association of dengue infection with hematological profile

The Mann- Whitney association of hematological profile between the dengue positive and negative groups is presented in Table 2. Briefly, in dengue positive group, erythrocytosis, high hematocrit, low MCH, low MCHC, decreased platelet count, decrease in TLC, high neutrophil, low lymphocyte count, low monocyte count, and low Eosinophil were observed than in dengue negative group.

3.3. Logistic regression and predictive markers

Binary logistic regression was used to assess the association between laboratory parameters and the outcomes (dengue positive and dengue negative). Independent variables – platelets (p<0.001, OR: 1.000, 95% CI: 1.0001.000), TLC (p<0.001, OR: 1.000, 95% CI: 1.0001.000), MCH (p<0.001, OR: 1.168, 95% CI: 1.075.268),MCHC(p<0.001,OR:4.089,95%CI:1.755-4.488), Neutrophil (p=0.003, OR: 0.821, 95% CI: 0.718-0.938) and Lymphocyte (p=0.035, OR: 0.865, 95% CI: 0.755-0.990) were added significantly to the model (Table 3).

Table1: Serological classification of dengue positive cases

Dengue Positive cases	NS1 only	N 40	Total
Single positive	IgM only	10	50
	IgG only	05	
	NS1+IgM	22	
Dual Positive	NS1+IgG	03	30
	IgM+ IgG	2	
Triple positive	NS1+IgM+IgG	08	10
	Total (Overall Positive)		**90**

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Table2: Hematological profile of dengue positive and negative cases

parameters	Dengue Negative(n= 90) Median(Q3-Q1)	Dengue Positive(n=90) Median (Q3-Q1)	P value
Age (years)	30 (47.0- 21.29)	32.0 (46.0 -24.0)	0.005
Hemoglobin (gm/dl)	16.1 (17.35-15.35)	16.4 (17.52- 15.0)	ns
RBC (X 10^{12}/L)	6.68 (6.99- 6.42)	6.98 (7.48- 6.58)	<0.001
HCT (%)	42.66 (48.15- 39.8)	48.5 (48.8- 40.5)	<0.001
MCV (fl)	88.9 (91.8- 85.9)	89.45 (93.99- 84.65)	ns
MCH (pg)	31.7 (32.6-30.7)	30.89 (32.17- 29.75)	<0.001
MCHC (gm/dl)	36.8 (33.1- 36.28)	35.07 (36.40-34.28)	<0.001
TLC (cells /cumm)	6525 (8265- 5595)	4412 (3512- 5812)	<0.001
Neutrophil (%)	66.1 (71- 60)	72 (81.79- 59)	<0.001
Lymphocyte (%)	30 (33.58- 26.58)	26 (39- 17)	<0.001
Monocyte (%)	8.8 (10- 7)	5 (9- 4)	<0.001
Eosinophil (%)	4 (4.48- 1)	1 (3- 0)	<0.001
Platelets (cells/cumm)	275000 (336000- 215000)	170000 (213000-146250)	<0.001

Table3: Binary logistic regression analysis for different parameters in overall dengue-positive patients

parameter	Univariate Analysis		Multivariate Analysis	
	ORC (95%CI)	p-value	ORA (95%CI)	p-value
Age	ns	ns		
HCT	0.910 (0.888- 0.929)	<0.001	ns	ns
MCH	1.299 (1.229- 1.378)	<0.001	1.168 (1.075- 1.268)	<0.001
MCHC	4.678 (2.394- 4.999)	<0.001	4.089 (1.755- 4.488)	<0.001
TLC	1.001 (1.000- 1.001)	<0.001	1.000 (1.000- 1.000)	<0.001
Neutrophil	0.970 (0.962- 0.979)	<0.001	0.821 (0.718- 0.938)	0.003
Lymphocyte	1.018 (1.008- 1.025)	0.017	0.865 (0.755- 0.990)	0.035
Monocyte	1.334 (1.280- 1.388)	<0.001	ns	ns
Eosinophil	1.694 (1.540- 1.862)	<0.001	ns	ns
Platelets	1.000 (1.000-1.000)	<0.001	1.000 (1.000- 1.000)	<0.001

DISCUSSION

Our data show that liver injury was almost universally present in a predominantly adult group of patients with DI. In most patients, liver dysfunction was mild to moderate, presenting primarily as elevation of serum aminotransferases. However, some patients had clinical manifestations of liver disease, namely jaundice, hepatomegaly and ascites. Two patients had findings consistent with acute liver failure.

Liver involvement is known to be common among children with DI. [8-16] However, reports of liver involvement in adult patients with DI are limited to individual case reports. [17] In infection with hepatotropic viruses such as hepatitis A or hepatitis B virus, the severity of liver involvement is related to age at infection, being more severe among adults than children. [18] Hepatitis A infection often remains either entirely asymptomatic or causes only a minor illness without any features to suggest liver injury. [19] Therefore, one may expect differences between adults and children in the frequency or severity of liver involvement in DI. Our study fills a lacuna in the existing literature by providing evidence of frequent liver involvement in adults with DI. However, the liver involvement in adults differed from that in children, in that palpable hepatomegaly was present in only about one-fourth of the patients, compared to its presence in 50%–80% of children. [20]

The biochemical pattern of liver injury in patients with DI was similar to that observed among patients with acute viral hepatitis—marked elevation of serum aminotransferases. The magnitude of elevation of ALT and AST levels was comparable, and no preferential elevation of one of these enzymes was observed. In view of this biochemical pattern, it is possible to confuse liver involvement in DI with typical acute viral hepatitis, especially in countries where outbreaks of hepatitis A and E are common. However, the presence of thrombocytopenia and persistence of fever after the appearance of jaundice should help to make a diagnosis of DI. Serological tests for infection with hepatotropic viruses and for dengue virus would help in confirming the aetiology of liver injury. The severity of liver injury is unlikely to be a pointer to the diagnosis since liver disease can be severe even in DI. It is noteworthy that 2 of our patients with DI presented with features of liver failure. In 2 fatal cases of DI, the histological findings in the liver were similar to those observed in infection due to known hepatotropic viruses; unfortunately, serological markers of hepatitis viruses had been tested in only 1 of these patients.

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Though ascites has previously been shown to occur in children with DI, its pathogenesis has not been studied. Based on high ascitic fluid protein concentration, this finding has been attributed to excessive leakage of plasma. However, SAAG, the most accurate parameter for assessing the presence of portal hypertension, was not measured. Our observation that the SAAG was >1.1 g/dl in 2 patients indicates that portal hypertension contributes to the development of ascites in patients with DI. Ascites has previously been reported in patients with acute viral hepatitis, and has been ascribed to increased portal pressure secondary to hepatocyte swelling and ballooning. [21] A similar mechanism may be responsible for ascites in patients with DI.

Among children, liver involvement has been reported to be more profound in severe forms of DI such as DHF/DSS. [22] In our study, evidence for more severe liver disease among such patients was less clear, though ALT elevation exceeding 5-fold the normal value was more frequent among patients with serious forms of DI. This finding could represent either a greater degree of liver damage due to the primary disease process or may reflect the effect of shock and consequent ischaemic hepatic injury. The higher mortality rates among patients with DHF and DSS than those with uncomplicated DI were possibly related to the severity of the underlying disease and not to differences in liver damage.

The mechanism of liver injury in DI remains unclear. Liver cells may be damaged through one or more of the following mechanisms: (i) direct cytopathic effect of the virus; (ii) killing of virus-infected cells by the host immune response; and (iii) a nonspecific effect of shock and hypotension. Our observation of a high frequency of liver injury among patients with uncomplicated DI in the absence of hypotension suggests that the injury is specific. The presence of dengue virus antigens and nucleic acid has been shown in liver tissue using immunohistochemistry, in situ hybridization and in situ polymerase chain reaction techniques. [23] However, it is unclear whether or not the virus multiplies in the hepatocytes. In recent years, dengue-specific CD4+ and CD8+ Tcells have been shown to play a part in the pathogenesis of severe forms of DI; occurrence of more severe liver injury in patients with complicated dengue may thus suggest a role for host immune responses in the causation of liver injury as well.

An apparent limitation of our study is our failure to obtain serological confirmation of the diagnosis of DI in nearly one-fifth of our patients. The lack of IgM anti-dengue antibodies in these patients was possibly related to testing during an early phase of illness. It is known that anti-dengue virus antibodies may not be present during the initial days of illness. [24] However, even in our seronegative patients, the presence of fever and thrombocytopenia in the epidemiological setting of an outbreak makes the diagnosis fairly certain.

CONCLUSION

In conclusion, liver injury is nearly universal in adult patients with DI. Though liver involvement is asymptomatic in a large majority, in some patients it leads to clinical manifestations of liver disease and may occasionally lead to acute liver failure and death. Care must be taken to not make a mistaken diagnosis of viral hepatitis. Further studies are needed to define the mechanisms of liver injury due to this infection.

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