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Research Article

Deranged liver among Sudanese Patients with Dengue Virus Infection in Port Sudan Teaching Hospital

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Abstract

Background: Deranged liver is a well-recognized feature of dengue infection, often demonstrated by coagulopathy and mild to moderate increase in transaminase levels although jaundice and fulminant hepatic failure are generally uncommon. **Objective:** This study aimed to evaluate the hepatic effect of dengue fever amongst Sudanese patients. **Materials and Methods:** A cross-sectional descriptive study recruited in Port Sudan teaching hospital in the period from February 2013 to June 2014. 334 cases of dengue along with 101 cases of control were enrolled. The rapid immune chromatographies test was used to confirm positive dengue cases and WHO criteria were used for classifying the dengue severity. Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level (FB), platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and C-reactive protein (CRP) were all measured. **Results:** PT, PTT, and FB were found to be significantly higher in the infected cohort when compared to the controls ($P < 0.0001$). PT was prolonged in 9%, PTT was prolonged in 12.6% and shortened by 5.4% of the patients, whereas hypofibrinogenemia in 18.3% and hyperfibrinogenemia in 67.4% of the patients. Bleeding was seen in 10.5% of patients and thrombocytopenia was detected in 83.5% of patients. Out of 334 patients, 101 (30.2%) had abnormal coagulation results. Of 101 patients, 72 were subjected mixing studies for PT and PTT that revealed deficiencies in factors VIII (35%), IX (10%), V (10%), X (19%), and XII (14%). 43.6% patients had elevated AST and 21.8% had elevated ALT. **Conclusion:** This study demonstrated that hepatic dysfunction may be attributed to dengue virus infection which evident by prolongation in PT and PTT as well as hypofibrinogenemia and factor deficiencies.

Keywords: Deranged liver, Dengue, DHF, Coagulation factors, Sudan

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1. Introduction

Dengue virus has recently become a major public health concern, particularly in tropical and subtropical countries, predominantly in urban and periurban areas [1]. The incidence of dengue has grown dramatically over the world in recent decades. Over 2.5 billion people of the world's population are now at risk from dengue [2]. WHO currently estimated there may be 50-100 million dengue infections worldwide every year [2]. The resurgence of dengue has been observed in Port Sudan, Red Sea State, Sudan and dengue outbreak have been frequently reported from different part of the State in both urban and rural populations [3, 4]. Dengue virus (DENV) is a mosquito-borne *Flavivirus* that is transmitted by mosquitoes such as *Aedes aegypti* or *Aedes albopictus*. Based on the antigenic difference, DENV can be divided into five different serotypes, DENV 1 – 5. The most serious manifestations of the infection are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [5, 6]. The degree of liver dysfunction varies from mild injury with an elevation of aminotransferase to even fulminant hepatic failure [7, 8]. Hepatic dysfunction in dengue infection may be attributed to direct viral effect on liver cells or as a consequence of dysregulation host immune responses against the virus [7]. Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor [9]. However, there is still not much work was done in the studied area regarding the liver changes of dengue infection. This study was conducted to evaluate the variations of liver dysfunction by measuring the level of the liver enzymes, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen (FB) level and coagulation mixing studies. The significance of this study is the importance of measuring the liver enzymes in the patients with dengue virus infection.

2. Materials and Methods

A cross-sectional descriptive study was conducted in the period from February 2013 to June 2014 at Port Sudan teaching hospital, Red Sea State, Sudan. Three hundred thirty-four patients who were positive for dengue infection attending the hospital and 101 healthy controls were enrolled in the study.

2.1. Inclusion and Exclusion Criteria

All patients with clinical features and serologically positive dengue infection were included. The sample taken before hemostatic agents and blood transfusion administrated to the patients. The exclusion criteria include patients with serologically negative dengue or any other disease.

2.2. Study Sample

The blood samples were collected from all of the studied population. 3 ml of blood was transferred to tri- sodium citrate buffer tube, 3 ml in plain containers and 3 ml treated with tri-potassium ethylene diamine tetra acetic acid (K_3EDTA). The samples under standard laboratory temperature were processed to obtain serum and platelet poor plasma by using a centrifugation. The analysis was performed by expert technologists.

Chemical tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP) were examined within 2 hours of collection and determined by NycoCard® method using NycoCard® READER II (SN 67498, Axis- Shield PoC AS, Oslo, Norway). Chemical tests were determined by (BioSystems Chemicals S. A Costa Brava, Barcelona (Spain), expiry at 8/2015).

Hematological tests: Platelet counts were done using an automated hematology analyzer (Sysmex KX-21N, B 7151, and MF 9/2008 Japan). Coagulation tests: PT, PTT and FB were examined within 4 hours of collection using a semi-automated blood coagulation analyzer (bio bas-1 manufactured by RAL for SPINREACT, SN 536, Spain-European Community). Coagulation tests were determined by (Biomed diagnostic reagent, Germany).

2.3. Definition of Dengue

Dengue is a disease caused by any one of five closely related dengue viruses (DENV-1, -2, -3, -4, and -5) [6]. The clinical spectrum of dengue classified to DF and DHF (DHF I, DHF II, DHF III and DHF IV) [10].

2.4. Criteria for Dengue Severity

Patients were classified as dengue fever, dengue hemorrhagic fever or dengue shock syndrome according to WHO guidelines. The laboratory diagnosis of dengue was established by the demonstration of IgM and IgG immune chromatography Rapid

diagnostic test (RDT) (BioTracer/BioFocus, REF: 17112, Exp.12/2015, Korea), sensitivity 95.6 and specificity 96.

2.5. Statistical Analysis

Laboratory data of PLT, coagulation tests, and chemical investigations of patients with DF, DHF were statistically tested by Independent-sample t test, Correlation, and Pearson Chi-square test, whichever was appropriate. A *P. value* less than 0.05 were considered statistically significant. The Statistical Package for Social Sciences (SPSS 20.0 version, IBN. Chicago, USA) was used for data analysis.

2.6. Ethical Considerations

This study was approved by the regional Ethical Review Committee (ERC), written informed consent was obtained from all of the patients.

3. Results

The total number of the confirmed dengue patients was 334. Of the 334 patients, (217) 65% were males and (117) 35% were female. In the control group, (64) 63.4% were males and (37) 36.6% were females. Minimum age of the patient was 3 years and maximum age was 80 years with the mean age being 30±15. Minimum age of control was 6 years and maximum age was 76 years with mean age 22±6.

The clinical findings have been summarized in Table 1. The clinical demographic manifestations of the studied group were fever (334,100%), headache (282, 84.4%), joint pain (262, 78.2%), backache (198, 59.3%), myalgia (156, 46.7%), retro-orbital pain (69, 20.7%), and rash (28, 8.4%). According to the WHO classification system most cases of the current study were dengue fever; followed by dengue hemorrhagic fever I (Table 1).

All of the patients (334) presented were screened for PT, PTT and FB. The difference between the patient group and the control group was found to be significant in prothrombin time, partial thromboplastin time, and fibrinogen level ($P < 0.0001$). Prothrombin time, partial thromboplastin time, and fibrinogen levels were higher in the patient group than in the control (Table 2). Thrombocytopenia was observed in (279/334; 83.5%) of the patients. 234 (81%) presented in DF cases and 45 (100%) presented in DHF cases. Bleeding manifestations were observed higher in DHF than in DF patients ($P < 0.0001$). Bleeding was recorded in 35 (10.5%) cases of all dengue patients (Table 3). Bleeding manifestations included hematuria in 19 (54.3%) cases,

hematemesis in 1 (2.9%), hemoptysis in 1 (2.9%), epistaxis in 5 (14.2%) cases, and gum bleeds in 9 (25.7%) cases.

PT was prolonged in 30 (9.0%) of the patients and normal in 304 (91%). PTT was prolonged in 42 (12.6%) of patients, shortened in 18 (5.4%) of patients, and normal in 274 (82%) of the patients. 8 (2.4%) patients had prolonged PT and PTT together. The reduced fibrinogen level was noted in 61 (18.3%), 48 (14.4%) patients had high fibrinogen level, and 225 (67.4%) was normal fibrinogen level (Table 3). Out of 61 patients with reduced fibrinogen 29 patients were associated with prolonged PT and PTT. There was a positive correlation between short PTT and high fibrinogen ($P < 0.0003$); this relationship could be interpreted as an acute phase response situation.

Out of 334 patients' positive dengue infection, 101 (30.2%) had abnormal coagulation results. 81 (80.2%) patients with DF and 20 (19.8%) patients with DHF were screened for special parameters such as AST, ALT, and CRP (Table 4). The transaminase liver enzymes were relatively higher in DHF than DF. 44 (43.6%) patients had an elevated level AST, while 22 (21.8%) patients had an elevated level ALT. C-reactive protein was significantly higher in DHF 20 (100%) patients than the DF 65 (80.3%) patients (Table 5). Of 101 patients 72 Correction tests for PT and PTT were performed. The corrected results indicate a deficient factor. 72 Mixing experimental studies for PT and PTT revealed deficiencies in factors VIII 25 (35%), IX, 7 (10%), V 7 (10%), X 14 (19%), II 9 (12%), and XII 10 (14%). This suggests the dysfunction of liver cells in respect to the decreased synthesis of these factors.

4. Discussion

Deranged liver function in dengue infection can be a result of the direct effect of the virus on liver cells or the unregulated host immune response against the virus. Hepatic dysfunction in dengue infection is often demonstrated by mild to moderate raising in transaminase enzyme levels [11]. Abnormal liver tests are generally present in the first days of clinical infection and peak during the second week of illness [12]. Aminotransferase levels are useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding. Liver enzyme elevation is a common feature in dengue infection [13]. Wang and Shyn reported that AST abnormality was predominantly high as compared to ALT; 91% and 72% respectively [14]. However, in this study, AST levels were equal to or greater than those of ALT levels in most infected patients, a finding that has also been reported earlier [5, 15]. Abnormal liver enzymes in dengue infection have been reported also by various authors and the levels varies from 36.4% - 96% [16]. Our study observed elevated AST in 43.2% of DF, 45% of DHF and elevated ALT in 21% of DF, 25% of DHF. The liver enzymes were significantly more common in DHF/DSS

Characteristics	Patients (n = 334)	Control (n = 101)	P. value
Age			
(mean ± SD)	30 ± 15	22 ± 6	0.0001
(Range)	3 – 80 y	6 – 76 y	
Sex			
Male	217 (65%)	64 (63.4%)	0.7262
Female	117 (35%)	37 (36.6%)	
Clinical diagnosis			
Dengue fever	289 (86.5%)		
DHF grade I	31 (9.3%)		
DHF grade II	12 (3.6%)		
DHF grade III	2 (0.6%)		
Clinical manifestations			
Rash (Purpura)	28 (8.4%)		0.0030
Fever	334 (100%)		0.0001
Joint pain	262 (78.4%)		0.0001
Backache	198 (59.3%)		0.0001
Headache	282 (84.4%)		0.0001
Myalgia	156 (46.7%)		0.0001
Retro-orbital pain	69 (20.7%)		0.0001
Bleeding manifestations	35 (10.5%)		0.0001
Epistaxis	5 (1.5%)		
Hematemesis	1 (0.3%)		
Hemoptysis	1 (0.3%)		
Hematuria	19 (5.7%)		
Bleeding gums	9 (2.7%)		

Table 1: The epidemiological and clinical feature of the studied population.

when compared to DF, a finding similar to other studies[17, 18]. Souza et al reported in large studies in Brazil, out of 1585 dengue cases, raised AST and ALT in 63.4% and 45% of patients respectively [19]. Jagadishkumar et al suggested that the higher incidence of more than 10-fold rise in liver enzymes was observed in children in comparison to adult. This may be due to that children are at higher risk of hepatic involvement [11]. AST levels rise more than ALT in case of dengue and this may be due to myositis,

Parameters	Test group Mean ± SD	Control group Mean ± SD	Median Test	Median Control	Range Test	Range Control	P.value
PT second	14.1± 2.1	13.3 ± 1.6	13.8	13.5	10–20.4	10-16.5	0.0001
PTT second	33.5 ± 9.7	29.6 ± 4.5	32.4	28.9	15–80.7	20-39	0.0001
FB g/dl	4.15 ± 6.99	3.26 ± 1.44	2.60	2.90	0.5 – 63.96	1.37-10.23	0.0001

Table 2: The difference between test and control in studied parameters.

Parameter	DF *n = 289*	DHF *n = 45*	P. value
Thrombocytopenia	234 (81%)	45 (100%)	0.0001
Bleeding manifest	10 (3.5%)	25 (55.6%)	0.0001
Prolong PT	27 (9.3%)	3 (6.7%)	0.0001
Prolong PTT	32 (11.1%)	10 (22.2%)	0.0001
Hypofibrinogenemia	48 (16.6%)	13 (28.9%)	0.0001
Hyperfibrinogenemia	40 (13.8%)	8 (17.8%)	0.1902

Table 3: General parameters among DF and DHF patients.

possibly related to coexisting myositis and released of AST from the injured muscle cells [12].

In the current study the prolonged PT values presented in 9% of the all cases and it was significantly more in DF (9.3%). Wong et al and Itha et al reported that the derangement in PT and PTT in 42.5% and 7% respectively of his cases [13, 20]. While the deranged PT and PTT in this study was 21.6%. This because that most of our cases are DF 86.5% unlike the above mentioned studies most of their cases are DHF and DSS. A correlation between the levels of AST and PTT shows a strong association between AST elevation and PTT prolonged time in dengue infection in our patients (P< 0.0003), this might seem to relate to the process of hepatic parenchymal damage than the biliary tract obstruction.

Parameters	Median	Mean ± SD	Range of test	Normal range
CRP	136 mg/l	125 ± 49	4 – 230	5 – 120 mg/l
AST	34 U/l	54 ± 69	5 – 480	Up to 40 U/l
ALT	22 U/l	34 ± 43	2 – 279	Up to 41 U/l

Table 4: Laboratory findings of specific parameters among the studied dengue patients.

Parameters	DF *n = 81*	DHF *n = 20*	P. value
High CRP	70 (86.4%)	17 (85%)	0.2873
High AST	35 (43.2%)	9 (45%)	0.9785
High ALT	17 (21%)	5 (25%)	0.6171

Table 5: Special parameters among DF and DHF patients.

Fulminant hepatic failure may occur because of acute hepatitis and massive necrosis of the liver, causing hepatic encephalopathy and even death [21]; this finding was not diagnosed in our patients.

With regard to CRP, the level was high in DHF patients. Nevertheless, this high circulating level of CRP is not correlated with the severity of illness and the occurrence of complications (P< 0.0966). A study by Shiann et al [22] in Taiwan showed that patients with dengue infection were more likely to have low CRP, which is different from our results, this difference may be due to the environmental factor and sample size numbered. In contrast, Juffrie et al [23] reported a high level of CRP in their study and Kutsuna et al [24] who reported that CRP is useful to indicate the dengue fever; our findings are consistent with them.

The advantage of this study is that it is prospective and only serological confirmed positive dengue infected patients were enrolled. The limitation of this study is that liver biopsy was not performed in any patients to confirm the diagnosis. This study could be considered a base for the future studies regarding the liver damage.

5. Conclusion

In summary, this study demonstrated that hepatic dysfunction may be attributed to dengue virus infection which evident by prolongation in PT and PTT as well as hypofibrinogenemia and factor deficiencies. The presence of bleeding may be useful in predicting the extent of liver involvement.

6. Acknowledgement

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7. Competing Interest

The author declares that they have no competing interests.

8. Availability of Data and Material

The data which are published are always reproducible by investigators

9. Ethics Approval

This study was approved by the regional ethical review committee (medical research ethics committee) ministry of health, Red Sea State, Sudan.

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