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Full Length Research Paper

A correlation study between clinical manifestations of dengue fever and the degree of liver injury

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Dengue virus caused an extensive epidemic in Portsudan, Red Sea State, Sudan extending from July to December 2009. The acute presentation, regarding liver injury, varies from mild or even no hepatitis to sever or even fulminant hepatic failure. Therefore, we measured the levels of liver enzymes, prothrombin time (PT), creatinin in dengue infection and compare them to the clinical presentation of the patients. 633 Patients were seen in the outpatient and inpatient departments of Portsudan teaching hospital, Portsudan, Red Sea State, Sudan in the period from July to December 2009. All of them were serologically confirmed dengue cases and were negative to heptotropic viruses (A, B, C &E), malaria, leptospira, typhoid and brucellosis. The degree of hepatic injury was established according to the alterations in the liver enzymes, prothrombin time and creatinin levels. Grade 0 - normal levels of liver enzymes; Grade 1 – mild elevation in the liver enzymes, not exceeding the double of reference value; Grade 2 - elevated liver enzymes, with the levels of the enzymes increased to more than three times the reference values; grade 3 - acute hepatitis, with liver enzymes levels increased to at least 10 times their normal values; Grade 4: evidence of hepatic failure (high PT) or hepato-renal involvement (high creatinin). In this study, there were 280 male and 353 female serologically confirmed dengue cases (total: 633), 63.8% presented mild alterations in the liver enzymes levels (grade 1), 17.9% presented grade 2 liver involvement, 3.9% of the patients had progressed to acute hepatitis (grade 3) and 1.1% had severe liver damage with fulminant hepatic failure. 50% of the renal impairment occurs in grade 3 liver damage and the other 50% in grade 4 liver damage. All cases of encephalopathy (100%) occur in grade 4 liver damage. Mild elevation of the liver enzymes was a common finding in dengue virus infected patients. There was a high relation between the degree of liver injury and presence of the complications. At least, the aspartate transeferase (AST) should be done regularly in the follow up of dengue patients in Portsudan.

Key words: Dengue virus, hepatitis, liver failure, Portsudan.

INTRODUCTION

Dengue virus (DENV) is a member of the Flaviviridae family, which include West Nile virus (WNV), yellow fever virus, Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (TBEV), among others (Lindenbach and Rice, 2003) Dengue is caused by four antigenically distinct viruses designated as Dengue virus type 1–4 (DENV 1–4) and is transmitted between vertebrate hosts by insect vectors. The most serious manifestations of the infection are Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). No effective vaccine or antiviral drug therapy is currently available against Dengue virus (Lindenbach and Rice, 2003). Dengue viral infection has been recognized as one of the world's biggest emerging epidemic. Throughout the tropics this infection has an annual incidence of 100 million cases of DF with another 250,000 cases of DHF and mortality rate of 24,000-25,000 per year (Gubler 2002a, b; Halstead, 1999). In the last years, Portsudan faced many out-breaks, one was reported in 2005.Since then, Portsudan has become an endemic area with dengue virus (Ali et al., 2005).

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Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms such as an uncomplicated fever (Whitehorn and Farrar, 2010; WHO, 2009; Reiter, 2010). Others have more severe illness (5%), and in a small proportion it is life-threatening (Whitehorn and Farrar, 2010; Reiter, 2010). The incubation period ranges from 3 to 14 days, but most often it is 4–7 days (Gubler, 2010). The characteristic symptoms of dengue are: a sudden-onset fever, headache (typically behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "break-bone fever", comes from the associated muscle and joints pains (Whitehorn and Farrar, 2010; Chen and Wilson, 2010).

Severe disease is marked by two problems: dysfunction of endothelium and disordered blood clotting (Varatharaj, 2010). Endothelial dysfunction leads to the leakage of fluid from the blood vessels into the chest and abdominal cavities, while coagulation disorder is responsible for the bleeding complications. Higher levels of virus in the blood and involvement of other organs (such as the liver) are associated with more severe disease (Martina et al., (2009). Dengue may occasionally affect several other body systems (Seneviratne et al., 2006). This may be either in isolation or along with the classic dengue symptoms (Martina et al. (2009). Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus. Other contributing factors include race, diabetes, hemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs (Seneviratne et al., 2006; George, 1997). Although there are isolated case reports of fulminant hepatic failure, the derangements in the transaminases are usually mild and self-limiting (Seneviratne et al., 2003). Although the number of patients affected by the virus is increasing each year, little work has been done in the studied area (regarding the pathogenisty, the liver changes and the complication of dengue infection). So, we aimed (in this study) to evaluate the degree of liver injury by measuring the level of the liver enzymes, PT and creatinin. These parameters were compared with the clinical presentation of the patients; to see how could the degree of liver damage was related to the complications of the disease. The first significance of this study, is increasing the awareness of the local health staff about the degree of severity of liver damage in dengue infected patients. The second, is the importance of measuring the liver enzymes (at least the aspartate transeferase- AST) in the follow up of dengue virus infection. Thirdly, this research form a base for future studies in the region regarding the outcome, the mortality, the hospital stay and the prognosis of dengue infection according to the level of liver damage.

METHODS

This study was conducted in the outpatient and inpatient departments of Portsudan teaching hospital, Portsudan, Sudan during the outbreak of dengue infection which occurs in the period from July to December 2009. Portsudan city is the capital of the Red sea state and it is the major sea port of the Sudan. The total number of the whole population was 739,300 according to the national census of 2002 with adjusted growth rate. There are four localities in this area (Port Sudan, Sinkat, Tokar and Halayib). Portsudan teaching hospital is a governmental hospital which is regarded as tertiary care hospital. The total number of beds is about 380, and the medical services are opened for all population with aid of the best professional staff in the region. In this descriptive study , all confirmed case of dengue virus were included. These patient were then classified according to their clinical presentation into classic, dengue hemorrhage, dengue shock or other complication (eg: encephalopathy, renal impairment, gastrointestinal bleeding and cholecystitis). Ethical clearance was approved from the local Ethical Review Committee.

All of the patients in this study were tested first for malaria, typhoid, leptospira and brucellosis: and they had negative results. Patient with positive tests of hepatitis A, B, C, E or even had recent history of infection with these hepato-tropic viruses are excluded from this research. All of the patients included in this work were confirmed dengue cases by serological (Enzyme-linked immunosorbent assay (ELISA) test NovaTec) detection of IgM or rising titer of IgG antibodies against the virus (98% sensitivity and 95% specificity).

To study the degree of liver damage, samples were collected into two blood containers. The first was plain container form which serum was extracted for assessment of the liver enzymes - aspartate transeferase (AST) and alanine transaminase (ALT) - and creatinin levels. The second was tri-sodium citrate container from which plasma was used to detect the PT level. The degree of liver damage was assessed according to the levels of the liver enzymes, PT and creatinin as follow: Grade 0 - normal levels of liver enzymes; Grade 1 – mild elevation in the liver enzymes, not exceeding the double of reference value; Grade 2 - elevated liver enzymes, with the levels of the enzymes increased to more than three times the reference values; grade 3 - acute hepatitis, with liver enzymes levels increased to at least 10 times their normal values; Grade 4: evidence of hepatic failure (high PT)or hepato-renal involvement (high creatinin).

The clinical data were collected on predesigned questionnaire which include gender, clinical findings, complications and laboratory test done.

Statistical analysis was done using statistical package for social science (SPSS) programme. Chi square test was used to compare categorical variables and Fischer exact test were applicable.

RESULTS

633 confirmed dengue patients were included in this study. 248 were male and 319 were female (male to female ratio was approximately 3:4). In this satudy,13.2% of the patients had no increase in the transaminases level (grade 0), 63.8% presented mild alterations in the liver enzymes levels (grade 1), 17.9% presented grade 2 liver involvement, 3.9% of the patients had progressed to acute hepatitis (grade 3) and 1.1% had severe liver damage with fulminant hepatic failure (Table 1). In 86% of the patients there was elevation of the liver enzymes. All of them (549 patients) had increase in the AST level. The change in the ALT was seen in 82% of the patients.

Most of the patients (567 patients) had features of dengue fever without complications. In this group, the common degree of liver damage (69%) was grade 1

Table 1. Relation between clinical presentation and the degree of liver injury in patients infected with dengue virus.

Clinical presentation	Number of patients	Males	Females	Grade 0 liver damage	Grade 1 liver damage	Grade 2 liver damage	Grade 3 liver damage	Grade 4 liver damage
Dengue fever	567	248	319	82	394	91	0	0
Dengue hemorrhage	28	15	13	2	6	12	8	0
Dengue shock syndrome	10	4	6	0	2	3	5	0
Gastro-intestinal bleeding	16	10	6	0	1	6	9	0
Encephalopathy	4	2	2	0	0	0	0	4
Cholecystitis	2	1	1	0	1	1	0	0
Renal impairment	6	0	6	0	0	0	3	3
Total	633	280	353	84(13.2%)	404(63.8%)	113(17.9%)	25(3.9%)	7(1.1%)

(that is, mild elevation in the liver enzymes). 28 patients presented with dengue hemorrhage and 12 of them (43%) had grade 2 liver injury. 10 patients presented with dengue shock syndrome. In this group, 5 patients (50%) had grade 3 liver injury. From the 16 patients presented with gastro-intestinal bleeding, 56% had grade 3 liver injury. 4 patients presented with encephalopathy and all of them had grade 4 liver damage. Of the 6 patient who were complicated by renal impairment, 50% had grade 3 and 50% had grade4 liver damage.

DISCUSSION

Dengue virus is among the commonest causes of febrile illnesses in Portsudan, Sudan (Ali et al., 2005). The importance of this study lies in that, it is the first documented research in this region of Africa which study the severity of liver damage in dengue infection. In this research we included dengue patients with mild symptoms seen in the outpatient department and sever cases who were admitted in the impatient units, so this study covers the mild as well as the severe cases of dengue virus infections.

To date, there are two hypothesis that explain the damage of the liver in dengue patients. The first is immune enhancement hypothesis. In 2004, Chen et al. reported that strong correlation was found between T cell activation and hepatic cellular infiltration in immunocompetent mice infected with dengue virus (Chen et al., 2004). They noted that the kinetics of liver enzyme elevation also correlated with that of T cell activation and suggested a relationship between T cell infiltration and elevation of liver enzymes (Chen et al., 2004). Chaturvedi et al. (1999) in their study detected the appearance of different helper cells cytokines in human white blood cells cultures infected in vitro with dengue virus type 2. In their study they have reported that during dengue infection; monocytes, B cells, T cells and mast cells produce large amounts of cytokines. Despite all this, role of host immunity in dengue infection is still very unclear (Chaturvedi at al., 1999). Unregulated host immune response may play some part in severity of dengue infection therefore by modifying the immune response, severe infection can be prevented (Seneviratne et al., 2006). The second hypothesis relates the damage in the liver to direct virulence of the virus (Seneviratne et al., 2006). According to these studies, we can hypothesize the same mechanism responsible for the liver damage occurs in our patients.

Liver damage with elevation of aminotransferases and reactive hepatitis was a common complication of dengue virus infection. Hence measurement of AST and ALT is mandatory to see the liver involvement (Souza et al., 2004). 86% of our patients had high AT level and 82% had high ALT level. However it was reported that AST abnormality was predominantly higher as compared to ALT; 91 and 72% respectively (Wong and Shen (2008). Another study done by Kuo et al. (1992) has shown approximately 90% of the AST abnormality in dengue patients. A different retrospective study among Thai patient in 2001 outbreak, reported liver dysfunction in 20 from 347 patients (5.8 %) with dengue infection (Wichmann et al., 2004). Our study is consistent with the results from Wong et al. and Kuo et al. (1992) studies. The difference results may be explained by the difference in the dengue virus type involved in their outbreak, or its hepatotoxicity (Wichmann et al., 2004). Other difference may be in the immune status of their patients or the days of collection of their serum

samples.

In this study, we noticed high relation between the degree of liver damage and the presence of the complications. In 71% of the patients having dengue hemorrhage sever degree of liver damage occur (Grades 2 and 3). We suggest a significant role of deranged liver functions in the causation of bleeding in addition to the thrombocytopenia. Sever degree of liver injury (Grades 2 and 3) also was found in 80% of dengue shock syndrome. All of the patients having encephalopathy had grade 4 liver damage. Encephalopathy in our patients may be due to fulminant hepatic failure or a high level of the virus that directly damage the brain. Involvement of the kidneys was also related the severity of liver damage, 50% with grade 3 and 50% with grade 4. Again this may be a part from hepato-renal syndrome or direct virus virulence.

Similar results to our work were seen in other countries. In Saudi Arabia, Khan et al. (2008) had made an association between high AST level and complications of dengue virus. In Taiwan, Kuo et al. (1992) has reported higher bleeding episodes in those who had high levels of AST, ALT and GGT. In Vietnam, Nguyen et al. (1997) reported that DHF may cause mild to moderate liver dysfunction in most cases; only some patients may suffer from acute liver failure leading to encephalopathy and death. A report from India done by Shah pointed to a high mortality in dengue patients with hepatitis and encephalopathy Shah (2008).

Conclusion

Mild elevation of the liver enzymes is a common feature of dengue infection. On the other hand, this could be severe to a degree of acute hepatitis or even to fulminant hepatic failure. There is high relation between the degree of liver damage and the appearance of the complications. Because Portsudan is one of the endemic areas with this virus, dengue infection should be one of the differential diagnosis of hepatitis (in the local hospitals protocol for diagnosis of hepatitis). At least the level of the AST should be assessed in the first visit and the follow up of all dengue infected patients. AST can be a useful surrogate marker to predict disease severity and bleeding outcome in dengue infection. The level of the other liver enzymes, PT, creatinin and electrolytes should be assessed in all severe cases of dengue infection.

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