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Dengue fever in Northern Pakistan: The Hepatic Implications

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Abstract

Background: **To gauge the clinical spectrum of dengue fever in northern Pakistan and to assess its hepatic implications**

Methods: **This prospective study was conducted at Rawalpindi General Hospital (now BBH), Rawalpindi from 1st Oct 2006 to 31st Dec 2008. It included all 264 patients suffering from dengue fever who presented during this period. Dengue infection was suspected if two or more of the following features in addition to fever were present: headache, retro-orbital pain, myalgias/arthralgias, scarlet/maculopapular rash, vomiting/epigastric pain and haemorrhagic manifestations. Blood samples were sent for dengue virus IgM. A blood complete picture, liver function tests, serum urea and creatinine, and urine R/E were also obtained. Specific evidence of liver involvement was also sought on examination.**

Results: **The 264 patients comprised of 146 males and 118 females. Age of patients ranged from 14 to 80 years. 220 patients were seen in the last three months of 2006, the time of the dengue epidemic. Fever and myalgias were present in all patients. Vomiting was seen in 223 (85%) and abdominal pain in 163 (62%) patients. A skin rash was present in 148 (56%) while 56 (21%) complained of joint pains and 53 (20%) of retro-orbital pain. 26 (10%) patients had a bleeding disposition and jaundice was noted in 6 (2%).**

Leukopenia and thrombocytopenia were present in all patients, while 254 (96%) had proteinuria. ALT was elevated in 163 (62%) and AST was raised in 135 (51%) patients.

Conclusion: **The liver is affected in a large number of cases of dengue fever. Liver function tests are useful to evaluate the degree of liver damage and markers such as AST and ALT may be used as parameters to assess severity.**

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Introduction

Dengue fever (DF) is an acute infectious disease of antiquity. It is probably the most important arthropod-borne viral disease in terms of human morbidity and mortality, with several million infections occurring annually for which no effective therapy exists. The clinical spectrum ranges from a self-limiting infection to more severe forms like dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) with a mortality rate of up to 40 percent.[1]

In the past twenty years, dengue has re-emerged with an expanded geographic distribution of both the virus and the mosquito vector, increased epidemic activity, the development of hyper endemicity (co-circulation of multiple serotypes) and the emergence of dengue haemorrhagic fever in new geographic regions. All four dengue serotypes are now endemic around the globe. The reasons for this resurgence and emergence of dengue haemorrhagic fever are complex and not fully understood. However, demographic, societal and public health infrastructure changes in the past 30 years seem to have contributed greatly.[2, 3]

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.[4, 5] However liver function abnormalities and associated pathologic findings are not always mentioned in dengue literature. Liver involvement may be characterised by pain in the right hypochondrium, hepatomegaly, varying degrees of jaundice and an increase in liver markers, mainly ALT and AST as found in acute hepatitis caused by A,B,C,D and E viruses. Pathologic findings include centrilobular necrosis, fatty change, kupffer cell hyperplasia, acidophilic bodies and monocyte infiltration.[6, 7]

In 2006, dengue fever reached epidemic proportions in Pakistan's largest city Karachi, and with mass northward movement of the working class to their homes for the Eid vacations, spread all over the country.[8] A large number of patients were also reported from Rawalpindi with Rawalpindi General Hospital bearing the brunt of the influx in the city. From October to December 2006 alone, 220 cases of DF and DHF were managed by us.

The purpose of this study was identify the presenting features and variance in clinical presentation of dengue fever, as well as to gauge the

spectrum of liver involvement in patients afflicted by the disease.

Patients and Methods

This Prospective Study was conducted at Rawalpindi General Hospital (now Benazir Bhutto Hospital), a tertiary care referral center and teaching hospital of Rawalpindi Medical College, Rawalpindi. It included 264 patients who presented with dengue fever from 1st October 2006 to 31st December 2008. All were more than 14 years of age and presented with an acute febrile illness. Dengue fever was suspected if two or more of the following features in addition to fever were present: headache ,retro –orbital pain, myalgias, arthralgias, scarlet /maculopapular rash, vomiting /epigastric pain and hemorrhagic manifestations. Laboratory investigation criteria were also laid down. Patients with acute febrile illness having leucopenia (TLC < 4.0X109/L) and/or thrombocytopaenia (Platelets < 150x109/L) and deranged transaminases were also worked up for dengue fever. For a definite diagnosis, blood samples were sent to National Institute of Health, Islamabad where Dengue virus IgM was performed by standardized ELISA method (Serum ELISA IgM Kit: sensitivity 86% specificity 100%). To avoid false negative results, it was ensured that patients had a history of fever of at least one week duration before collecting the blood samples for the test. Within two months of commencement of the study, this kit became available at our hospital and blood samples were also tested here.

A blood complete picture, liver function tests, serum urea and creatinine, prothrombin time and urine R/E were also obtained. Considering the overlapping signs and symptoms and endemic nature of typhoid fever and malaria in our region, all patients also underwent appropriate smear or serological tests for these diseases (Widal /Typhidot and malarial parasite smears for three consecutive days). Once a definite diagnosis of Dengue fever was established, only symptomatic treatment was advised and the patients monitored for DHF and DSS, using current guidelines of WHO and Pan American Health Organization as under.[9]

Dengue haemorrhagic fever was diagnosed when the patient fulfilled the following clinical criteria: Fever, any haemorrhagic manifestation, thrombocytopaenia (platelet count 100,000/ml or less) and objective evidence of increased capillary permeability. The latter was documented by either haemoconcentration (an increase in haematocrit of 20% or greater from average, or decrease by an equivalent amount from base line after intravenous fluid therapy), pleural or abdominal effusion (by radiography /ultrasonography) or hypoalbuminemia / hypoproteinemia. When the only haemorrhagic manifestation was provoked (by a tourniquet test) the patient was categorised as a case of Grade I Dengue Haemorrhagic fever. A spontaneous hemorrhage, even if mild, indicated Grade II illness. Grade III and IV DHF (incipient and frank circulatory failure respectively) were taken to represent dengue shock syndrome.

All clinical presentations and laboratory findings were recorded in the study Specific evidence of liver involvement was also sought on examination. Descriptive analysis was performed using SPSS 10.0 programmer.

Results

The 264 patients studied comprised 146 males and 118 females (male to female ratio 1.2:1). Age of patients ranged from 14 to 80 years. The mean age was 30.4 years. The highest incidence occurred in those aged between 14 to 35 years with 177 (67%) patients figuring in this age range.

Table 1: Clinical features in patients (n=264)

Clinical Features	Patients	Percentage
Fever	264	100%
Myalgias	264	100%
Vomiting	223	85%
Abdominal pain	163	62%
Skin rash	148	56%
Joint pains	56	21%
Retro-orbital pain	53	20%
Headache	42	16%
Bleeding manifestation	26	10%
Sore throat	13	5%
Dry cough	13	5%
Jaundice	6	2%
Productive cough	2	0.8%

The most common clinical features were fever and myalgias which were present in all 264 patients (Table 1). Fever was high grade, ranging from 101 to 105 F, intermittent and accompanied by chills & rigors. Vomiting was seen in 223(85%), abdominal pain in 163(62%) and a skin rash in 148(56%) patients. 56(21%) patients complained of joint pains, 53(20%) of retro-orbital pain while 42(16%) had severe headache. 26(10%) patients had a bleeding disposition in the form of epistaxis, haematemesis or melena. Jaundice

was noted in 6(2%). Other symptoms included sore throat and cough.

Laboratory findings revealed leukopenia and thrombocytopenia in all patients (table 2). TLC ranged from 1.5 TO 3.3 X 10^9/L. PCV ranged from 21.5 to 62. Proteinuria was detected in 254(96%) patients. A raised ALT was seen in 163(62%) and raised AST in 135(51%) patients. Bilirubin was elevated in 8(3%) patients.

Of the 264 patients 259(98%) subsequently recovered. Those with DHF and DSS were managed with platelet concentrates and blood transfusions. All five (2.7%) mortalities had DHF or DSS and occurred in the period 2007 to 2008. All 220 patients seen in the last 3 months of 2006 recovered and were eventually discharged from hospital. This included twenty two patients with DHF.

Table 2: Laboratory findings (n=264)

Lab findings	Patients	Percentage
Leukopenia	264	100%
Thrombocytopenia	264	100%
Proteinuria	254	96%
Elevated ALT	163	62%
Elevated AST	135	51%
Elevated Bilirubin	8	3%

Discussion

In 1994, dengue haemorrhagic fever was first reported in Pakistan from Karachi.[10] Sporadic cases continued to surface from Haripur in 2003 and Attock in 2004 until the 2006 epidemic which also originated from Karachi and spread north. The emergence and re-emergence of DF and DHF in northern Pakistan seems related to the increase in density and geographic distribution of the vector and increase in the rate and geographic range of virus transmission. Illiteracy, poverty, sub-standard living conditions plus deterioration of health systems and mosquito control programmes have all been blamed. The increase in air travel allows the movement of different serotypes, strains and genotypes of the virus from one region to another. Individuals in the viremic phase are able to introduce a new virus into a susceptible population.

WHO reported that a temperature rise of 1 to 2° C could result in an increase of the risk population by several hundred million, with 20,000 to 30,000 more fatal cases annually world-wide.[9] The implications of global warming are glaringly obvious. Most of our patients, who reported in the autumn of 2006, came from relatively cleaner, greener, suburban areas of the city and beyond. However as winter set in, the numbers declined but now the majority presented from congested and warmer areas of Rawalpindi.

The involvement of liver in the pathogenesis of dengue virus has been indicated by clinical signs of hepatomegaly, abnormal liver function, pathological findings and detection of viral antigens.[11-14] A transient liver transaminase elevation is commonly found. Predictive factors for liver damage have been identified which include DHF, secondary infection, thrombocytopenia, high haematocrit, female sex and children.[15, 16] Wong and Shen found elevated levels of AST in 90.6% of their 127 patients and raised ALT levels in 71.1%, while both ALT and AST were increased in 70.9%. Low levels of globulin were observed in 14.4% and low albumin levels in 16.5% of their patients.[15]

Dengue virus-induced damage to hepatocytes, hypoxia, shock or associated liver disease have all been postulated to be the pathogenic mechanisms for elevated transaminases.[16] Daniel et al[17] noted hepatomegaly in 17.6% of their 250 patients. Bilirubin was above 2 mg% in 9.7% and AST was raised in 84%. No mortality was observed in those with a normal AST while it was 4.1% in patients with a raised AST. This suggests a worse outcome in patients with a raised AST. Ascites was detected by ultrasound in 12% of their patients. 62.4% had abdominal pain, a symptom which is predominately seen in early leak phase and is attributed to hepatomegaly and serosal inflammation.[17]

Sharma et al noted abdominal pain in 38%and hepatomegaly in 12% of their series. However transaminases were elevated in 90% of patients.[18] Elevated transaminases were also noted in 66% of 80 patients with DF in Jeddah, Saudi Arabia[19] which corresponds to our findings. Wiwanitkit reported liver dysfunction in 35% of 191 patients. Hepatic encephalopathy was seen in 2.6% (5 cases) but no fatalities resulted.[20]

A strong correlation has been reported between T cell activation and hepatic cellular infiltration in immunocompetent mice infected with dengue virus. It was noted that liver enzyme elevation correlated with T cell infiltration and activation.[21] Fatty change, centrilobular necrosis and monocyte infiltration in the portal tract have been reported in humans.[20]

The secreted form of dengue virus non-structural protein NS 1 is also thought to be important. It is endocytosed by human phagocytes and accumulates in endosomes.[22] it has been speculated

that this protein could play a role in liver damage and that the amount of NS1 accumulated would depend on the virulence of each particular strain and serotype infecting the liver cells.[23] Receptors in hepatocytes have also been shown to have affinity for dengue virus serotype 1.[12]

Paracetamol is usually administered in dengue infection to treat fever. However, paracetamol may increase in the risk of hepatic injury and severe liver damage has also been demonstrated.[24]

In conclusion, Pakistan can now be counted among the countries harbouring dengue virus and its vector. The liver, though not the main target organ is affected in a large number of cases. Liver function tests are useful to evaluate the degree of liver damage and markers such as AST and ALT may be used as parameters to assess severity. They should be taken from the 3rd up to the 8th day of illness. If clinically indicated they can be repeated at least 3 weeks after discharge. Hepatitis serology is useful for patients with suspected hepatitis or persistent liver disease on follow-up. Routine hepatobiliary ultrasound in acute dengue infection is not recommended. On recovery, sonographic findings including ascites resolve spontaneously.

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