NEUROLOGICAL MANIFESTATIONS OF DENGUE FEVER

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ABSTRACT

Objective: To observe the pattern of neurological complications in hospitalized cases of dengue fever (DF) and study the association of various clinical parameters with neurological manifestations of DF.

Study Design: A cross-sectional descriptive study.

Place and Duration of Study: CMH Lahore, from August 2011 to November 2011.

Patients and Methods: The study was based on clinical profile and outcome of 640 adult hospitalized patients of DF. They were categorized on the basis of neurological involvement into DF, with and without neurological manifestations. After clinical evaluation, blood samples were taken for a complete blood count, urea, creatinine, sodium, potassium, bilirubin, alanine transaminase (ALT), prothrombin time (PT) and activated partial thromboplastin time (APTT). SPSS 18 was used for statistical analysis of clinical data.

Results: Thirty eight out of 640 hospitalized DF patients had significant neurological involvement. The age of the patients ranged from 13 to 84 years with an average of 44.5 ± 19.2 years in DF cases with neurological manifestations and 38.0 ± 14.1 years in DF cases without neurological manifestations. Most of the cases with neurological involvement fulfilled the World Health Organization (WHO) criteria for dengue haemorrhagic fever (62.4%). Systolic and diastolic blood pressures were significantly low, platelet counts were also very low and serum ALT levels significantly high in DF patients with neurological involvement. Case fatality rate was 26.3% in DF cases with neurological involvement as compared to 1.6% in the rest of the DF patients without neurological involvement (p<0.001).

Conclusion: Recognition of dengue infection as causative agent in patients presenting with neurological complications is important in endemic areas to avoid potentially toxic and costly treatments.

Keywords: Dengue fever, encephalopathy, neurological manifestations.

INTRODUCTION

Almost four out of every ten people in the world are at risk for dengue virus infection[1]. The features of infection range from an asymptomatic state to a severe hemorrhagic disorder with multisystem involvement. Encephalopathy and neurologic complications are important features of this disease. The relationship between dengue hemorrhagic fever (DHF) and neurological disturbances was first described in 1976, and since then several publications have added to the information available on this disease[2-4]. Many neurological manifestations of dengue infection have been described to include headache, seizure, depressed sensorium, behavioral disorders, neck stiffness, delirium, paralysis, cranial nerve palsies and coma. Previously, reports of neurological manifestations in dengue infection had been referred to as encephalopathy rather than encephalitis because attempts to demonstrate direct invasion of the central nervous system (CNS) by dengue virus had failed. Therefore, the pathophysiology of these neurological manifestations was thought to be secondary to prolonged DHF/DSS as opposed to encephalitis, which is defined as a localized invasion of the CNS[5]. Various physiological events were thought to lead to encephalopathy such as cerebral oedema, cerebral haemorrhage, hyponatraemia, fulminant hepatic failure[6], cerebral anoxia, micro-capillary haemorrhage and release of toxic products[7]. Recently people have shown that elevated level of interleukin 6 (IL-6) and IL-8 is associated with different neurological

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manifestations and poor outcome in patients of DF[8] and hypertrophy of white matter astrocytes in patients of DF even in the absence of increased vascular leakage[9]. However most of the studies strongly support the hypothesis of direct neuro-virulence of the dengue virus. The detection of neuro-virulence markers may contribute to establish a prognosis, the disease control and vaccine development[10].

There was a huge outbreak of DHF at Lahore and surrounding areas of Punjab in 2011. We are presenting an account of various common and uncommon neurological features encountered in the hospitalized cases of DF. The aim was to study the neurological features due to DF in these patients and relationship of neurological presentation with other clinical parameters.

PATIENTS AND METHODS

This is a cross-sectional descriptive study based on the hospital records of 640 indoor adult patients of dengue fever. All these patients were hospitalized in acute medical wards at CMH Lahore from August to November 2011 with a strong clinical suspicion of DF. The criteria of hospitalization for clinically suspected DF patients were uncontrolled vomiting, moderate to severe abdominal pain, moderate to severe dehydration and shock, platelet count less than 50x109/l, haemorrhagic manifestations and altered consciousness. Patients with clinical presentation suggestive of DF and supported by positive reactivity of dengue specific IgM antibody were labeled as confirmed DF. Patients with suggestive clinical features and bicytopenia, negative reactivity for dengue specific IgM antibody were labeled as probable DF. Probable DF included those cases also, in which serological confirmation was not considered necessary due to an obvious clinical diagnosis in the setting of an epidemic. All the other patients of acute febrile illnesses due to malaria, urinary tract infections, respiratory illness or an unidentified cause, with a least suspicion of DF were not included in the study. Both confirmed and probable DF cases were included in this study. Patients were also categorized according to severity into dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) cases according to WHO guidelines[8]. We have studied the descriptive statistics in these patients by dividing them into two groups of DF with and without neurological presentation and compared various clinical variables in these two groups.

All these adult cases had been hospitalized according to the clinical criteria mentioned above. Age, sex, symptoms (fever, headache, bodyaches, abdominal pain, haemorrhagic manifestations), signs (purpura) and their duration, systolic and diastolic blood pressure were noted. After detailed clinical evaluation, blood samples were taken for a complete blood count and serum levels of urea, creatinine, sodium, potassium, bilirubin and alanine aminotransferase (ALT). Prothrombin time (PT) and activated partial thromboplastine time (APTT) were also checked. Clinical parameters were compared in two groups, DF with and without neurological manifestations. Blood counts were serially monitored till the platelet counts started showing a rising trend and reached the safe limits.

Hematological profile was done on Sysmex KX-21 haematology analyzer. Serum bilirubin, ALT and creatinine were done on Vitalab Selectra E chemistry analyzer and electrolytes were measured with Easylyte Na/K electrolytes analyzer. Dengue specific IgM antibody reactivity was determined by standard enzyme linked immunosorbent assay (ELISA) technique.

Patients were managed according to standard protocols with intravenous fluids and symptomatic treatment. Transfusion with platelets concentrate, whole blood and fresh frozen plasma were considered necessary only when patients showed active bleeding with very low platelet counts and/or evidence of coagulopathy (deranged PT and APTT). Patients were discharged from the hospital when they

were afebrile, symptomatically better and showed an upward trend in platelet count.

SPSS 18 was used for statistical analysis. In data analysis, mean and standard deviation were calculated for quantitative variables and categorical variables were presented by frequency and percentages. Independent sample t-test was used to see the statistical significance of difference of means between various continuous variables in two groups of patients. Chi square test was used when two dichotomous categorical variables were compared. Statistical significance of the difference in various variables between the two groups was considered significant when *p*-value was less than 0.05.

RESULTS

The analysis of 640 patients is presented (table-I) by dividing them into two groups of DF with neurological manifestations, n=38 (5.9%) and DF without neurological manifestations n=602 (94%). The age of the patients ranged from 13 to 84 years with an average of 44.5 ± 19.2 years in neurological DF and 38.0 ± 14.1 years in DF cases without neurological manifestations. Headache and vomiting were present in all the patients with neurological DF. DHF criterion was fulfilled by 23 (60.5%) of neurological DF and 136 (22.6%) of DF cases without neurological manifestations ($p<0.001$). Systolic and diastolic blood pressures, both were significantly low in DF cases with neurological involvement. Platelet counts were very low ($p=0.005$) and serum ALT significantly high ($p=0.001$) in DF patients with neurological involvement as compared to the other group. Dengue shock syndrome was noted

Table-I: Descriptive analysis of dengue fever patients with and without neurological involvement.

	DF without Neurological Manifestations (n=602)	DF with Neurological Manifestations(n=38)	*p*-value
Age	38.0 ± 14.1	44.5 ± 19.2	0.04
Women (n=63)	56 (88.9%)	7 (11.1%)	0.8
Men (n=577)	546 (94.6%)	31 (5.4%)	
Duration of symptoms (days)	5.1 ± 1.4	5.4 ± 2.1	0.3
Fever	602 (100%)	38 (100%)	
Headache	524 (87%)	38 (100%)	0.01
Bodyaches	564 (93.6%)	35 (92%)	0.7
Vomiting	524 (87%)	38 (100%)	0.01
Abdominal pain	460 (76.4%)	30 (78.9%)	0.7
Haemorrhagic Manifestations	136 (22.6%)	23 (60.5%)	<0.001
Purpura	100 (16.6%)	6 (15.8%)	0.9
Systolic blood pressure (mm Hg)	105.8 ± 9.8	99.3 ± 19.4	0.03
Diastolic blood pressure (mm Hg)	69.8 ± 7.6	64.9 ± 14.5	0.04
Hemoglobin (g/dl)	13.8 ± 1.5	13.4 ± 2.0	0.1
Hematocrit (mm)	41.5 ± 4.5	40.4 ± 6.1	0.1
Total leucocyte count(x 109/litre)	3.6 ± 1.3	4.7 ± 2.9	0.02
Platelet count(x 109/litre)	32.7 ± 21.8	22.6 ± 17.2	0.005
Coagulopathy	132 (21.9%)	20 (52.6%)	<0.001
ALT (units/litre)	80.2 ± 82.9	182.2 ± 389.5	0.001
Confirmed Dengue	256 (42.5%)	25 (65.7%)	0.005
DSS	17 (2.8%)	7 (18.4%)	<0.001
Hospitalization (days)	3.7 ± 1.4	5.6 ± 4.8	0.02
Mortality	10 (1.6%)	10 (26.3%)	<0.001

in 7 (18.6%) cases of DF with neurological involvement and 17 (2.8%) patients of DF without neurological involvement (p<0.001). Average hospital stay was prolonged and case fatality rate was very high in DF cases with neurological involvement (table-I).

We have summarized various important neurological features in our patients of DF with neurological involvement in table-II. Ten patients presented with paraparesis of acute onset with preceding constitutional symptoms of dengue fever. All of these patients had hypokalemia and raised creatine phosphokinase (CPK) levels. Paraparesis improved with potassium replacement. Twelve of our patients presented with intracranial bleeding. There was rapid cognitive decline with seizures and focal neurological signs. Four patients were labeled as cases of encephalitis, who had focal neurology associated with ischemic structural injury on neuroimaging. One of these patients had changes typical of brainstem infarct. Another lady developed loss of vision in one eye, probably due to retinal vasculitis. MRI brain suggested her to hospital stay. Two patients presented with status epilepticus and comatosed state. One patient had findings typical of brachial plexopathy which was later on confirmed by nerve conduction study as axonal injury. Headache was present in almost all of our DF cases and mild neuropsychiatric manifestations were also common, so these neurological symptoms were not used in our classification of DF with and without neurological involvement. The commonest neuropsychiatric manifestations which we noticed were emotional incontinence, insomnia lasting for days, mild confusional state and severe mental fatigue alongwith physical fatigue on recovery.

DISCUSSION

Our study is important as it demonstrates that almost all patients with severe DF had some neurological manifestation, e.g. headache. All of these patients responded to potassium replacement. Acute neuromuscular weakness is a known complication of DF and hypokalemia is probably the commonest cause. Dengue-associated hypokalemic paralysis often has a

Table-II: Neurological manifestations in dengue fever patients.

Neurological Manifestations	Frequency (Percentage in DF cases with neurologicalmanifestations)
Flaccid paraparesis	10 (26.3%)
Intracranial bleeding	12 (31.6%)
Dengue Encephalopathy	11 (28.9%)
Dengue Encephalitis	4 (10.5%)
Brachial plexopathy	1 (2.6%)
Retinal vasculitis	1 (2.6%)
GTC seizures	8 (21%)
Status Epilepticus	2 (5.2%)
Frank Psychosis	1 (2.6%)

be suffering from dengue encephalitis. Many other patients of DF, who developed altered consciousness and cognitive decline with or without some focal neurological deficit, had no defect on neuroimaging and cerebrospinal fluid (CSF) examination. They were labeled as cases of encephalopathy. Almost eight patients of neurological DF developed seizures during rapidly evolving course; benign nature; excellent response to potassium; and, often leads to diagnostic confusion with other dengue-associated neuromuscular disorders[11]. A recent study from India reported 12 cases of acute neuromuscular weakness, 10 of whom had hypokalemia, one had Guillain Barre syndrome (GBS) and the other had myositis[12]. Another

recent study reported three cases of GBS associated with acute DF during a large outbreak in New Caledonia[13]. We did not encounter any case of GBS in association with DF.

Twelve of our patients presented with intracranial hemorrhage. There was rapid cognitive decline with associated seizures and focal neurologic signs. Ten of these patients had acute symptoms of DF but two were diagnosed afterwards with typical appearance of rash and serological markers. Haemorrhagic encephalopathy is not very common in DHF[14], but we recorded a fairly high number of cases with intracranial bleeding in patients of DHF (7.5%). We had four patients of dengue encephalitis, who had altered consciousness with focal neurology and neuroimaging suggestive of viral encephalitis. Dengue has classically been thought not to be neurotropic[15]. However, the discovery of dengue virus and anti-dengue Ig M in the CSF of patients with encephalopathy suggests that dengue is capable of causing CNS infection[2,7]. The evidence from various published studies suggest dengue encephalitis to be a distinct clinical entity and the proposed definition is, "fever, headache, reduced consciousness, not explained by acute liver failure, shock, electrolyte derangement and intracranial haemorrhage, with a laboratory finding of dengue virus or IgM in serum or CSF and neuroimaging suggestive of viral encephalitis"[16,17]. Dengue fever is now considered a frequent or leading cause of encephalitis in some of the endemic regions[18]. There were many patients who were having focal neurology but neuroimaging and CSF did not reveal significant findings. They were labeled as having dengue encephalopathy. Encephalopathy is considered the most common neurological manifestation of dengue hemorrhagic fever (DHF). Its pathophysiology is multi-factorial and the contributing factors could be cerebral edema, hyponatremia, hepatic failure, renal failure and cerebral hypoxia[19]. Most of these patients had good recovery with supportive care. Neuropsychiatric manifestations are very common in dengue fever as it is primarily a neurotropic virus. Major manifestations which we observed were emotional incontinence, insomnia lasting for days, frank psychotic behavior, and severe mental and physical fatigue on recovery. However one patient had findings typical of brachial plexopathy which was confirmed lateron on EMG/NCS as axonal injury. He did not make a good recovery. Brachial neuritis is a rare association with dengue fever, reported first time in literature by Verma recently[20]. One of our patients had retinal vasculitis. She also had dengue encephalitis as evidenced on MRI brain. She gradually recovered from effects of vasculitis but vision in her eye did not return. Her vasculitis screening was negative and there was no clinical or serological evidence of any infection like syphilis, tuberculosis or brucellosis. All patients having neurological manifestations underwent these investigations.

CONCLUSION

Recognition of dengue infection as causative agent in patients presenting with neurological complications is important especially in endemic areas to avoid potentially toxic and costly treatments.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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