NEUROLOGICAL MANIFESTATIONS OF DENGUE FEVER: A CASE SERIES OF 10 PATIENTS

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ABSTRACT

Dengue is a mosquito-borne flavivirus and a rapidly growing tropical disease in the world. It continues to be one of the significant causes of morbidity and mortality globally. Dengue viruses (DENV) have experienced an outburst of neurologic case series in recent years. A widespread range of neurological manifestations including encephalopathy, acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome (GBS), cranial nerve palsies, transverse myelitis, and myositis have been documented following dengue infection. Here, we report 10 cases of dengue fever in association with other neurological abnormalities. We also conducted an extensive review of the literature to elucidate neurological complications following dengue infection. These unusual manifestations are usually overlooked, and we tried to fill the knowledge gaps in our study. From this case series we conclude that different neurological manifestations can be associated with Dengue virus infection.

Key Words: Dengue, Neurological complications, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Transverse Myelitis, Myositis.

INTRODUCTION

Dengue virus (DENV) is one of the most common acute viral illnesses in the tropics, threatening up to one-third of the global population. Dengue fever impacts almost 4 billion people around the world, with around 100 million cases of symptomatic dengue arising each year (1, 2). More than 70 percent of the world's illness burden is borne by Asia, dengue fever affects nearly 390 million people worldwide every year. Almost 500,000 of them suffer from a serious illness, with approximately 5% of them dying as a result (3). Dengue fever has been reported in Pakistan 15,719 times so far this year (as of October 13th, 2021), with 34 individuals dying as a result of the virus (4). Presentation ranges from asymptomatic dengue infection to multisystem involvement leading to multiorgan dysfunction, shock, and death. Anomalous symptoms of dengue infection and neurological indications were first reported in 1976 (5). Neurological complications in the context of dengue infections are becoming more commonly documented, with rates ranging from 0.5 percent to 20% (6) . Direct neuronal invasion, immune-mediated neuronal destruction, and systemic metabolic changes lead to CNS manifestation in dengue infection (7).

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Research Design:

Non-probability consecutive sampling technique was used to collect the cases for the case series.

Case 1

A 22-year-old man presented with a recent history of dengue fever followed by progressively altered sensorium. On examination, the patient was vitally stable. His Glasgow Coma Scale (GCS) was 7/15 E1 V2 M4. He had no signs of meningeal irritation and focal neurological deficit. Investigations revealed a positive dengue IgM and IgG, however, NS1 was negative. Complete blood count and metabolic profile was normal. Few Small hypodense regions in bilateral temporal lobes were discovered during an urgent Noncontrast computerized tomography (NCCT) scan. To evaluate it further Contrast-enhanced Magnetic resonance imaging (CEMRI) was performed, which indicated bilateral hypointense white matter changes on T1 that were hyperintense on T2 and FLAIR. Moreover, multiple hyperintensities were seen in the brain stem, centrum semiovale, medial temporal lobes, and bilateral periventricular white matter in FLAIR and T2 sequences. The diffusion was limited in the DWI/ADC pattern. There was no post-contrast enhancement visible. There was no discernible mass impact or mid-line change. He was intubated and managed in ICU due to his poor GCS. Keeping in view dengue-related ADEM, he was given methylprednisolone 1 g IV once a day as a high-dose steroid. However, the patient's condition deteriorated, GCS dropped, and he began to show signs of increased intracranial pressure. Unfortunately, he died on the fourth day of his arrival.

Case 2

A 57-year-old hypertensive woman was transferred from another hospital due to a history of worsening consciousness levels during the previous four days. She had dengue fever 20 days ago, the fever subsided in 3 days, and she remained normal for about 10days. 14 days after the dengue infection, she progressively became drowsy. She was taken to the hospital where her condition rapidly deteriorated in a couple of days. On arrival at our hospital, her BP was 170/100, Pulse 54/min, RR was 10/min shallow breathing pattern. Her GCS was 6/15, and plantar responses were equivocal on both sides. Pupils were non-reactive to light. Basic lab work was insignificant. Dengue serology IgG and IgM were positive. Multiple hyperintense signals were found on an MRI brain on T2 and FLAIR images in both frontoparietal lobes, especially on the right side. The cerebellum and pons also had a few T2/FLAIR hyperintense lesions. On the DWI/ADC picture, they displayed diffusion limitation and showed enhancement on the contrast image. There was a midline shift of 8mm (about 0.31 in) towards the left side. The likely possibility was post dengue ADEM. She was intubated and managed in ICU. Steroid pulse therapy was initiated but the patient has already gone into an irreversible state. She died on 2nd day of admission.

Case 3

An 18-year-old man with no previous co-morbidities and a history of recent dengue infection (two weeks ago) presented with lower limb weakness, and urinary and fecal retention. Following that, the patient had paralysis of the lower limbs along with cervical discomfort. The patient was oriented in time, place, and person and his higher mental functions were intact. There was flaccid paralysis in both lower limbs on neurological evaluation. Power in lower limbs of grade 1/5. However, reflexes of the lower limbs were intact. There was a sensory level up to T8. The upper limbs had 3/5 power with intact reflexes and sensations. Cranial nerves were normal. Baseline labs were normal. IgG dengue was positive. His MRI spine revealed Diffuse abnormal hyperintense signals seen in the cervical spinal cord from craniometrical junction to C7 vertebral level evident on T2 W1 / STIR along with mild cord expansion affecting the same segment. AntiMoG Antibodies were positive. Diagnosis of post dengue Transverse Myelitis with positive anti-MOG antibodies was made. He was treated with intravenous steroids (Pulse therapy). Failed to respond to this therapy, and he was offered five sessions of plasma exchange. There was slight improvement at discharge but in one month follow up he had significant improvement in his functional status.

Case 4

A 35-year-old man complained of a high-grade fever. The fever was intermittently associated with rigors and chills, as well as myalgias and arthralgias. The fever subsided in 3 days, but he developed gradually progressive limb weakness in the lower limbs. On Examination, he had flaccid paralysis (Power in UL 4/5, LL 2/5) with areflexia in all limbs. His investigations revealed positive serum dengue IgM antibodies. CSF study showed albuminocytologic dissociation. A Nerve conduction study was done which indicated sensory-motor demyelinating polyradiculoneuropathy. He was diagnosed with a case of dengue-related Guillain-Barre syndrome, and he was offered 4 sessions of therapeutic plasma exchange. He improved and on 2 weeks' follow-up he was completely recovered.

Case 5

A 39-year-old man with no past comorbidities arrived at the Outpatient department (OPD) with lower limb weakness, which started after a preceding history of dengue fever. Examination revealed a Power of 4/5 in upper limbs and 2/5 in lower limbs. There was generalized areflexia. Sensory and cranial nerve examination was normal. Blood count and routine biochemistry were normal. Dengue serology IgM was positive. The nerve conduction study was suggestive of a demyelinating neuropathy, Dengue virus associated GBS was considered, and he was offered 4 sessions of plasma exchange, he showed good recovery with it.

Case 6

A 49-year-old woman diagnosed case of dengue fever with Multiorgan dysfunction was transferred from some other hospital on the 4th day of febrile illness. On arrival, she was in compensated for shock, however fully conscious and oriented. Her labs showed pancytopenia (Hb 9.1 (MCV 88), TLC 3.1, Plt 98000. Dengue NS1 and IgM were positive. Bilirubin 2.1mg/dl, ALT 523IU, Urea 150mg/dl, Creatinine 2.1 mg/dl. She was admitted to ICU and was managed as per the protocol of complicated dengue fever. She developed irritability, irrelevant talk, altered sensorium, and confusion on the 5th day, subsequently, her conscious level deteriorated. She was put on ventilator support because of low GCS. CT scan brain was done that was normal. The

neurological impairment was attributed to dengue encephalopathy. She was managed for ongoing metabolic abnormalities, but she did not respond. On the 7th day of her illness, her blood pressure started declining, despite inotropic support, she progressed into circulatory failure and died.

Case 7

A 2-year-old kid had a five-day history of Fever and a 1-day history of drowsiness. On arrival at the Emergency Department, her temperature was 39 C; her pulse was 24/per minute, and her blood pressure was recorded at 109/76 mm of Hg. She was unresponsive to the verbal stimulus however she was able to localize pain. The planter response was equivocal on the left side. The rest of the examination was normal. Her investigations revealed positive serum dengue IgM antibodies with low hematocrit and platelet count. The rest of the blood chemistry was normal. MRI revealed subtle T2 and FLAIR high signals in the cortical and subcortical region of the bilateral frontal and right medial temporal lobe, the right medial temporal lobe also showed restriction on DWI. No post-contrast enhancement was seen. Clinical, laboratory, and imaging findings supported the diagnosis of dengue encephalitis. She was managed conservatively with fluid resuscitation according to standard protocol. She started improving, at the 4th day of admission her consciousness level Improved but she had weakness on the left side of her body. Her hematocrit and platelets got too normal.

Case 8

A 5-year-old child was presented to the emergency department with the chief complaint of fever, decreased oral intake, and irritability for 1 week. She developed an episode of generalized tonic colonic fits. On arrival at the Emergency Department, the child was drowsy. On examination, there was no neck rigidity or focal neurological deficit. Baseline investigations showed positive dengue NS1 antigen, and a low platelet count of 96,000 rest of the labs were unremarkable. The patient was admitted, and an MRI brain was planned which showed symmetrical T2 and FLAIR high signals in the bilateral basal ganglia, pons, and left cingulate gyrus showing subtle restricted diffusion on DWI images. It was diagnosed as dengue encephalitis. The patient was started on conservative management, she showed marked improvement in her symptoms.

Case 9

A 28-year-old male patient with no comorbidities presented to us with complaints of acute onset weakness in all four limbs. He also gave a history of high-grade intermittent fever for the last 2days. On examination, he was febrile with relative bradycardia. The power in both upper and lower limbs was ⅖ and ⅕, respectively. Reflexes were absent in all four limbs. Sensory and cranial nerves examination was normal. His investigations were done which revealed positive dengue NS1, however, cell counts, and hematocrit were normal. His potassium was low 1.9mmol/dl. Dengue-related hypokalemic paralysis was the working diagnosis. He was admitted to HDU, and IV potassium replacement as per standard protocol was made. For the next 24 hours, his weakness improved and so did the potassium. He was switched to oral potassium replacement once his potassium got 3mmol/l. On discharge, he was completely recovered.

Case 10

A 30-year-old male patient presented to the emergency department with complaints of generalized body aches, severe weakness in lower limbs along with nausea and vomiting. He had no prior co-morbidities. He also had a history of high-grade fever a few days back. On examination power in upper and lower limbs was 4/5 and 3/5 respectively. Muscle tenderness was present. Deep tendon reflexes were intact. The rest of the neurological examination was unremarkable. His investigations showed positive dengue NS1 antigen and low serum potassium of 2.81mmol/l. Creatinine phosphokinase (CPK) was 4899 IU. This led to the diagnosis of dengue-related myositis. He was managed with IV fluids and oral potassium replacement. Serial CPK showed a declining trend over the next 2 days. His symptoms improved and he was discharged on the 4th day.

Discussion

Dengue fever can manifest itself in several neurological manifestations. Acute disseminated Encephalomyelitis (ADEM) is a monophasic acute inflammatory demyelinating illness that has been observed in the context of dengue virus infection (8). ADEM appears within a short period (averaging 5.6 days) following the beginning of dengue signs(9). Though ADEM was stated as a rare condition, the incidence could be higher because of the high global burden of dengue infection. Multiple cases of Dengue-related ADEM have been identified in recent years(10, 11) (12). Although

there is no proven therapy for dengue related ADEM, steroid usage or plasma exchange can be helpful during its active phase (6). In our case series, we described two cases of dengue related ADEM. The course of the disease was aggressive and nonresponsive to the standard treatment in our patients.

The link between transverse myelitis and dengue virus is unusual, implying either a rapid onset of contagious myelopathy or an immune-mediated mechanism in which the virus works as a "trigger" for an inflammatory process that targets myelin sheath cells. The spinal cord involvement in these patients might be a partly phenotypic expression of ADEM post viral, an idiopathic inflammatory demyelinating illness associated with infections or immunizations(7). In literature, few cases have been documented in this regard. The extent of cord involvement and outcome was variable in different cases. A couple of cases have been mentioned in the literature that had positive aquaporin antibodies (13). Our case had positive anti-MOG antibodies that have not been documented in literature before. Whether the presence of antibodies in dengue is coincidental or permissive is to be elaborated yet.

Guillain-Barré Syndrome (GBS) is an autoimmune disease characterized by a rapid onset of paralysis, initiated by inflammatory demyelination(14). GBS is a complication that uncommonly occurs with dengue virus infection (15). Around 20 case reports of GBS linked to dengue illness have been published in the literature. Most of the instances involved children, with only a few adults (15-17). 1–19 days after the beginning of dengue fever, neurologic symptoms appear. GBS appears early in Dengue fever, with an atypical course, according to Simon et al. The average period from fever to neurological manifestations was 2 days, with a range of 1 to 3 days in their report (18).One patient with dengue-related Miller Fisher syndrome is also documented (19). Asymptomatic dengue virus infection can cause GBS, according to Umapathi et al., who discovered four GBS patients following a diagnosis of dengue, including three with acute inflammatory demyelinating polyneuropathy and one with acute motor axonal neuropathy (20). In randomized clinical studies, plasma exchange appears to be more favorable than conservative therapy (15). Our cases had NCS proven demyelinating neuropathy and had a complete recovery with plasma exchange.

Encephalitis is a severe form of dengue infection. According to Soares et al., Dengue fever is assumed to be the most common cause of encephalitis, with normal CSF analysis in 75% of patients in a dengue-endemic location (21). MRI brain can help make the diagnosis in clinically suspected scenarios (22). Treatment is symptomatic and the prognosis is typically good. Dengue Virus can lead to neurological manifestations more typically than previously known, and may constitute a large, underreported reason for viral encephalitis in the tropics. Inside the literature, the words “encephalopathy” and “encephalitis” have been used interchangeably. For this purpose, a correct interpretation of neurological manifestations, CSF analysis, and MRI of the brain and spinal cord are required to document neuro-dengue. We have reported cases of both encephalopathy and encephalitis in this case series.

Dengue myositis is being frequently reported in recent years. The clinical range is wide, ranging from moderate asymmetrical lower-extremity weakness to abrupt progressive severe limb and trunk paralysis, as well as lung failure(23, 24). The diagnosis becomes challenging because weakness in dengue-related myositis is uncommon and myalgias are usually taken as a part of the disease course. However, dengue myositis is said to be a benign and self-limiting infection in pediatric studies (25, 26). In adult patients, dengue myositis usually leads to severe rhabdomyolysis(27-29). Sangle et al. reported a case of a 16-year-old girl with dengue shock syndrome who was presented with myocarditis and myositis. Symptomatic treatment and rehabilitation were given, and she recovered well at discharge after 1 month of hospitalization [24]. Dengue can produce chronic and significant myositis, according to Finsterer et al., which is alleviated following corticosteroid therapy (29). Our patients had an uneventful recovery from myositis.

Dengue-associated hypokalemic paralysis has been acknowledged by various authors; however, most of the research was based on small case series or particular case reports. Maurya and co-authors reported 12 dengue patients with hypokalemic paralysis and found that potassium treatment helped them recover completely and quickly (30). It has been proposed that high creatine phosphokinase levels are produced by hypokalemia-induced vasoconstriction and muscle ischemia (31). In another study of 12 patients with severe neuromuscular weakness during a dengue outbreak, 10 of the patients had hypokalemia, whereas one patient had GBS and the other had myositis (32)

It was a single centered study, which can be one of the limitations of the study.

CONCLUSION

Dengue should be added to the differential prognosis of acute febrile disorder with neurological presentations in dengue-endemic international locations and individuals with a history of recent travel to a pandemic vicinity. Many neurological symptoms of dengue were recorded, ranging—with a tremendous overlap—from encephalitis and encephalopathy to immune-mediated disorders and muscle involvement. The latest data shows that the dengue virus may have a neuro-invasive potential. Dengue fever may sometimes bring on neurological symptoms, despite the fact that these manifestations are rather uncommon.

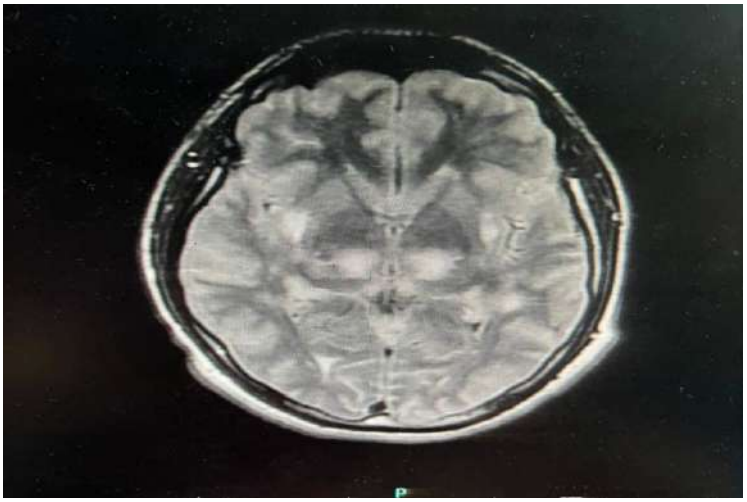

Figure 1 ADEM

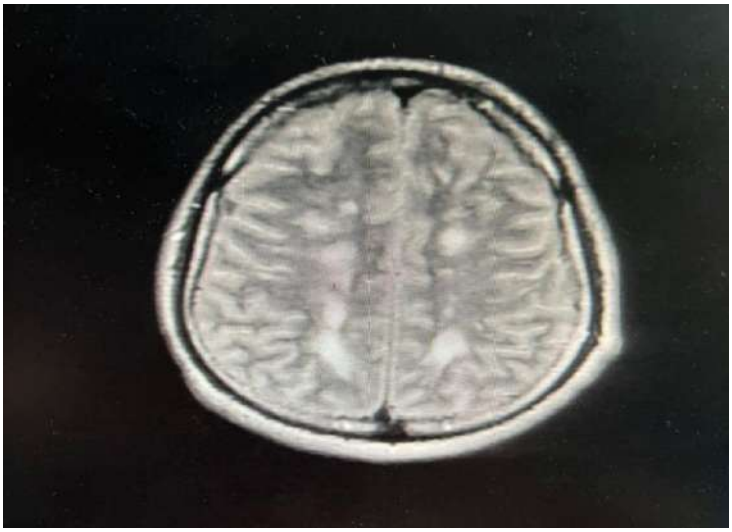

Figure 2 ADEM

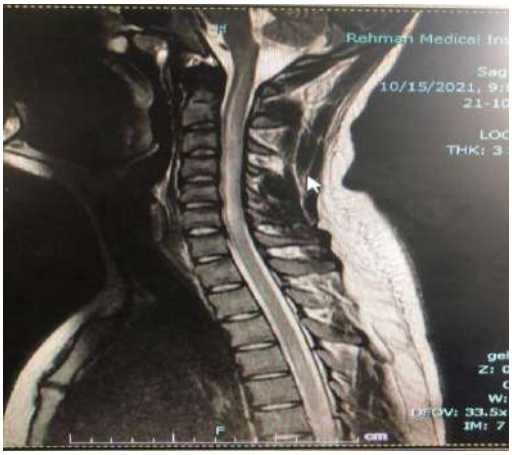

Figure 3 Transverse myelitis

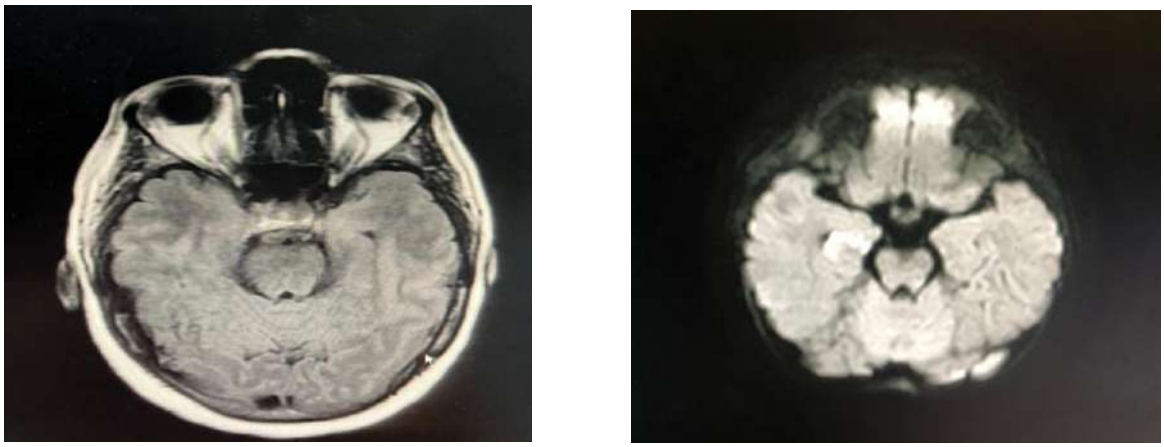

Figure 4 Case no 7

DECLARATIONS

Conflicts of Interests: Nil

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