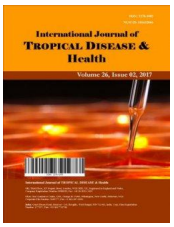

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Expanded Dengue Syndrome - A Lesson Learnt

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Authors' contributions

This work was carried out in collaboration between all authors. Author Arun Agarwal was the attending consultant in the case and contributed to the conception, design, draft, analysis, revision and final approval of the work to be published. Author PS was the primary consultant in the case. Author Aakanksha Agarwal contributed to the revision of the manuscript, grammar and literature search for the case study. Author GT was the medical officer involved in taking care of the patient in HDU. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Dengue virus (DV) is omnipresent, globally distributed flavivirus and is primarily transmitted by the Aedes aegypti mosquito, found through-out the tropical and subtropical regions of over 100 countries. Unusual manifestations of Dengue fever (DF) with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection have been increasingly reported in dengue hemorrhagic fever (DHF) and also in dengue patients who do not have evidence of plasma leakage. Expanded dengue syndrome is a new term added into World Health Organization (WHO) classification system to incorporate this wide spectrum of unusual manifestations. We report a case of tropical fever that presented as suspected brain stroke with seizures and later diagnosed to have dengue fever-expanded dengue syndrome. The presentation, diagnostic dilemma and management are discussed.

Keywords: Dengue fever (DF); dengue hemorrhagic fever (DHF); expanded dengue syndrome (EDS); neurological dysfunctions; ecchymosis.

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1. INTRODUCTION

Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome. Most of the symptomatic dengue infections follows an uncomplicated course and mild or severe organ involvement may be found in DF/DHF. However, complications and unusual manifestations of DF/DHF are increasingly being reported from across the globe due to the rising disease burden. They are commonly associated with co-morbidities and other co-infections. As per World Health Organization (WHO), clinical and systemic, atypical manifestations observed in EDS are as follows [1]:

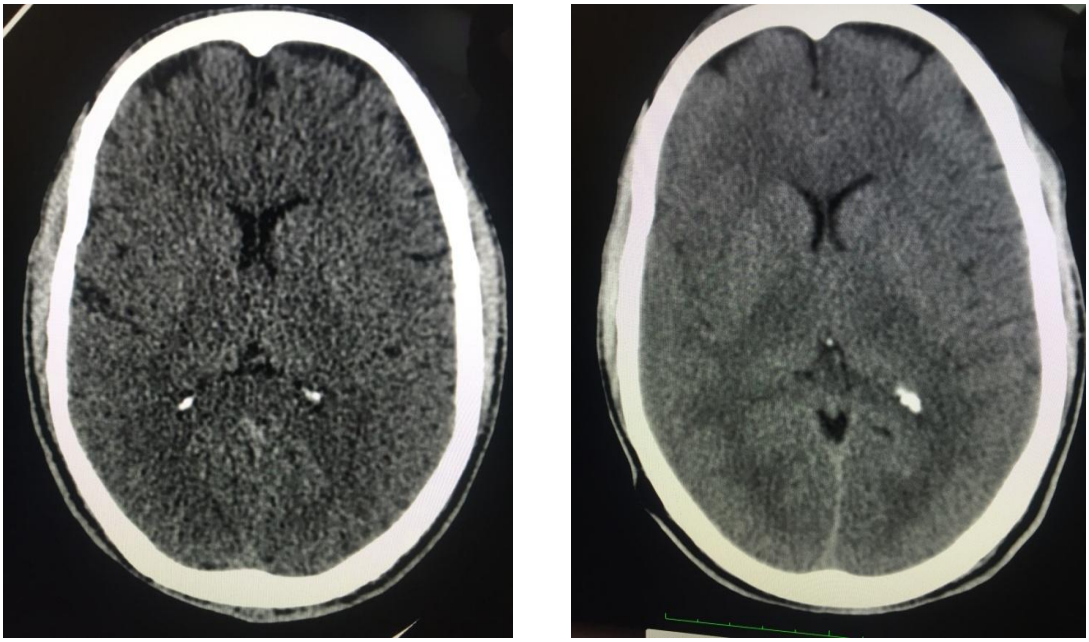
1) Central nervous system (CNS) involvement: Encephalopathy, encephalitis, febrile seizures and intracranial bleed.
2) Gastro intestinal involvement: Acute Hepatitis, fulminant hepatic failure, cholecystitis, cholangitis and acute pancreatitis.
3) Renal involvement: Acute renal failure, hemolytic uremic syndrome and acute tubular necrosis.
4) Cardiac involvement: Cardiac arrhythmia, cardiomyopathy, myocarditis and pericardial effusion.
5) Respiratory: Pulmonary oedema, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage and Pleural effusion.
6) Eye: Conjunctiva bleed, macular hemorrhage, visual impairment, optic neuritis.

Besides above mentioned atypical manifestations, various case series and case reports with neurological features [2,3], neuromuscular complications [4], sub acute thyroiditis [5], hemophagocytic syndrome [6,7], overt thyrotoxicosis [8], vasculitic skin lesions [9], pancreatitis with hemothorax [10], and thromboembolic events [11] have also been described in literature. Dengue fever is classically associated with many neurological dysfunctions which include headache, dizziness, sleeplessness, somnolence, restlessness, mental irritability, depression, and altered sensorium such as lethargy, confusion or coma. Seizures, neck stiffness and paresis are less commonly described.

There are many case reports of dengue encephalitis in pediatric patients but only few among adult patients. We report a case that had no co-morbidity or co-infection, and presented with mental obtundation, localizing signs, doubtful history of seizure, and had a normal non-contrast computerized tomography (NCCT) of brain. He was afebrile and was suspected to have occlusive stroke. Option of thrombolytic therapy for brain stroke was discussed and was refused by attendants for financial reasons. He was finally diagnosed to have DHF-EDS.

2. CASE REPORT

Mr. KB., 40 year's male was brought by his neighbors to the triage at Narayana Multispecialty Hospital, Jaipur, on 09.11.2017 at 4 pm. He was drowsy, with the history of being found unconscious in home about 20 minutes back by them. Immediate family members were not available for detailed history. On examination his body temperature was 98.6°F, pulse 69/minute and regular, BP 125/78 mm Hg, respiratory rate 20/minute, and oxygen saturation 96%. He was drowsy and disoriented, bleeding from left angle of mouth, and decreased movements of left side of body with extensor plantar response. Rest of the general and systemic examination was unremarkable. NCCT brain was done and it was unremarkable (Fig. 1A). A possibility of a seizure with a tongue bite could not be ruled out. Option of thrombolysis with a possibility of occlusive stroke in view of left sided weakness, left plantar extensor response, altered sensorium and a normal NCCT brain was discussed with the attendant's. However, it was refused by them. He was given intravenous levitiracetam, fosphenytoin and anti platelet drugs (aspirin and clopidogrel) in triage along with supportive treatment and shifted to high dependency unit (HDU) for observation and further work-up. In HDU he had an episode of generalized tonic clonic seizure and intravenous sodium valproate was given. A repeat NCCT brain was done on 10.11.2017 and it was also unremarkable (Fig. 1B). By now his routine blood counts, biochemistry and urine examination were available which showed severe thrombocytopenia, mild transaminitis, and hypoalbuminemia. On further questioning with attendants who were available by then it was found that he had fever for one day about 5 days back. Since it was only for a day, they did not realize that it could be a significant history and did not mention it. He also complained of headache. Dengue serology was done by a rapid solid phase immune-chromatographic method for the qualitative detection of dengue



A B

Fig. 1. NCCT brain dated 09.11.2017 and 10.09.2017

NS1 (non structural protein 1) antigen and antibodies (IgM and IgG). He tested positive for dengue NS1 antigen. CSF was not done in view of severe thrombocytopenia. His electroencephalogram (Fig. 2) was normal. An Internal medicine consult was sought and he was further evaluated. His investigations are mentioned in Tables 1 and 2. Ultrasonography done showed evidence of capillary leak with mild ascites and peri-cholecystic edema. On 11.11.2017 bilateral periorbital area was ecchymosed (Fig. 3) and subconjunctival bleeding was noticed. He was diagnosed as a case of dengue hemorrhagic fever with neurological dysfunction- Dengue encephalopathy (Expanded dengue syndrome) and managed with anti seizure drugs as mentioned, 2 units of single donor platelet (SDP), pantoprazole, ondansetron, and supportive treatment. He was discharged on 15.11.2017 with platelet count showing rising trend, transaminitis settling towards normal, and in stable condition on levitiracetam, phenytoin sodium and supportive treatment. Follow up after one month had been done and he is medically fit with normal blood counts and liver function tests.

3. DISCUSSION

Dengue is the second most common mosquito-borne disease affecting human beings. Dengue virus is a mosquito borne single positive-stranded RNA virus of the family Flaviviridae. Five serotypes of the virus have been found and all of them can cause the full spectrum of disease. The four closely related dengue viruses which follow the human cycle are — DV-1, DV-2, DV-3, and DV-4. The fifth variant DV-5 was isolated in October 2013 [12]. DV-5 serotype follows the sylvatic (wild animals) cycle. There is no indication of the presence of DV-5 in India [13]. Several studies report that DEN-2 and DEN-3 have the highest propensity to cause neurologic complications [14,15,16].

Dengue illness is associated with many neurological dysfunctions and can be life threatening. One of the earliest reports of CNS manifestations in DF was by Rush during the 1780 epidemic in Philadelphia. Since then many case reports and case series with CNS manifestations in dengue illness have been reported in literature. In 2009, WHO endorsed new guidelines and for the first time neurological manifestations were considered in the clinical case classification for severe dengue. These have been noted in up to 0·5-21% of patients with dengue illness admitted to hospital [2]. Neurological manifestations with a possible overlap can be of four types: dengue encephalopathy (for example caused by hepatic failure or metabolic disorders), dengue

encephalitis (caused by direct virus invasion), neuromuscular complications (for example guillain-barré syndrome or transient muscle dysfunctions), and neuro-ophthalmic involvement [2]. The common encephalitic features include fever, headache, mental obtundation, seizures, meningism, extensor plantars, frontal release signs, abnormal posturing, facial nerve palsy and quadriparesis [17].

The discovery of dengue virus [15,18,19] and anti-dengue IgM [18,19,20,21] in the cerebrospinal fluid (CSF) of patients with dengue encephalopathy has been reported and suggests direct invasion of CNS by the dengue virus. Additionally it is attributed to capillary leakage leading to cerebral edema, hemorrhage, disseminated intravascular coagulation (DIC), shock, and metabolic and electrolyte disturbances. The definitive diagnosis of DF rests with the laboratory diagnostic methods. Brain imaging with MRI is the modality of choice. It helps in excluding differential diagnosis and may show features of viral encephalitis such as cerebral edema, white matter changes, evidence of breakdown of blood brain barrier on contrast MRI in acute stages. It may even be normal or have only subtle changes which may be difficult to interpret.

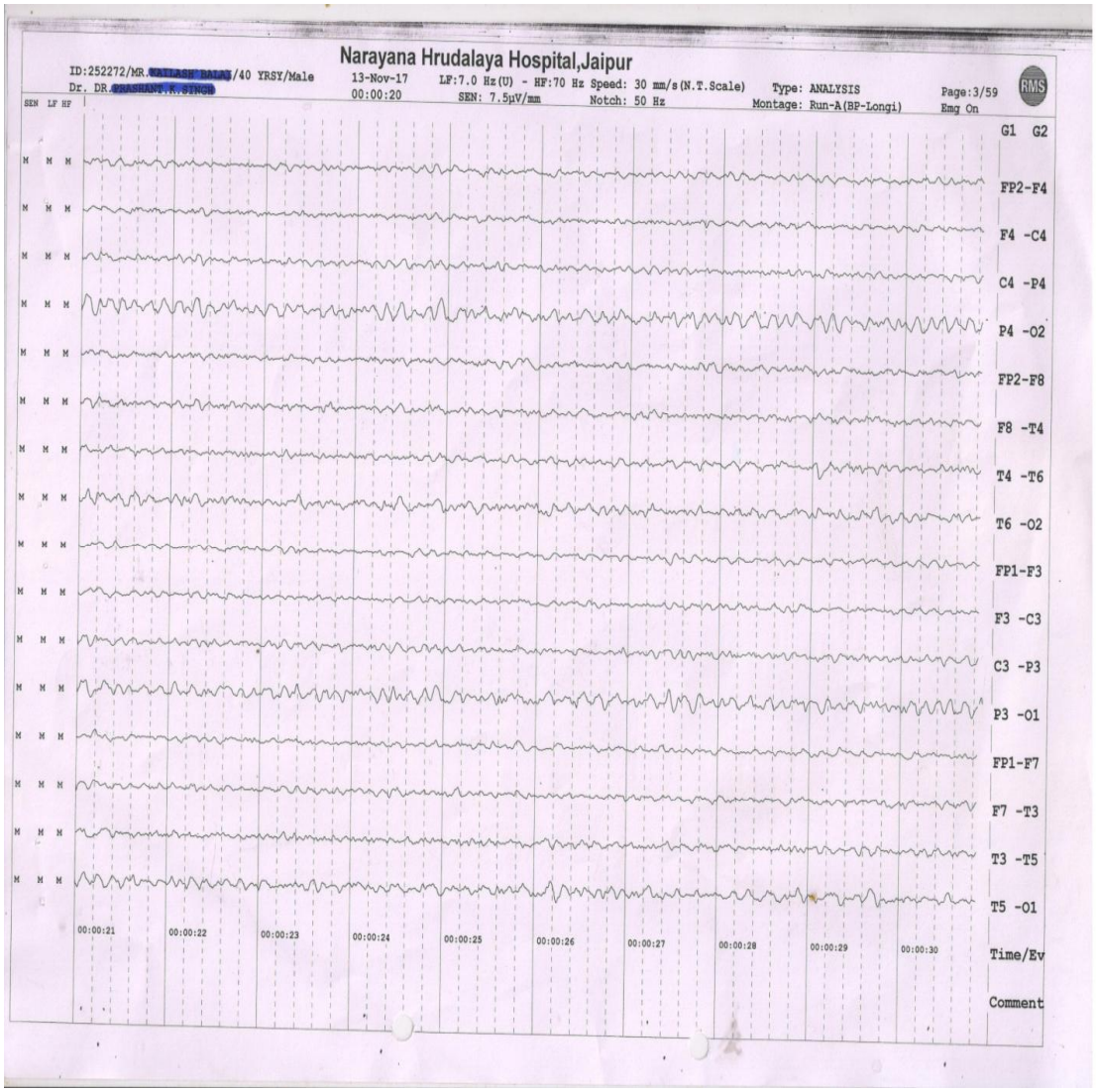


Fig. 2. EEG dated Nov.13, 2017

Table 1. Hematology and biochemistry

Date	Hb (g/dl)	TLC ($X10^3$/ul)	Platelet count ($X10^3$/ul)	AST	ALT	Serum albumin	GGT (U/L)	Serum creatinine (mg/dl)	S. electrolytes (Sodium/potassium/ chloride (meq/L)
Normal Values	13-17	4.0-10.0	150-400	15-37	30-65	3.4-5.0	15-85	0.8-1.3	135-150/ 3.5-5.0/ 95-106
09.11.2017	15.2	3.2	13	98.1	62.4	2.87	33.8	0.82	141.9/4.6/ 105.5
10.11.2017			13						
11.11.2017			34(M) 30(E)						
12.11.2017			22(M) 27(E)	102.7	74.1				
13.11.2017			25(M) 33(E)						
14.11.2017 15.11.2017			40 60	68	52.4	2.14	87.5		

Hb: Hemoglobin; TLC: Total leukocyte count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT:Gamma glutamyl transferase; g/dl: grams per decilitre; ul: microlitre; U/L:Unit per litre; mg/dl: miligrams per decilitre; meq/L:milliequivalents per decilitre

Table 2. Other investigations

Date	Test	Report
09.11.2017	ABO Blood Group	O (-)
	NCCT Brain	Normal
10.11.2017	NCCT Brain	Normal
	USG abdomen	Mild free fluid in peritoneal cavity and peri cholecystic edema.
	ABG	pH 7.471,pCO2 41.1,pO2 70.3,sO2 96.1%,BE 5.7mmol/L,HCO3 29.3 mmol/L
	ECG	Tracings within normal limits
	Dengue NS1 antigen	Detected
	Dengue IgM antibody	Not detected
	Dengue IgG antibody	Not detected
	MP	Negative
	Serology Profile	HBsAg,HIV,and anti HCV antibody non reactive
11.11.2017	Urine routine examination	Unremarkable
13.11.2017	EEG	Normal record

NCCT: Non contrast computerized tomography; USG: Ultrasonography; ABG: Arterial blood gas; ECG: Electocardiogram; NS1: Non structural protein 1; IgM: Immunoglobulin M; IgG: Immunoglobulin G; MP: Malaria parasite; EEG: Electroencephalography; HBsAg: Hepatitis B surface antigen; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus

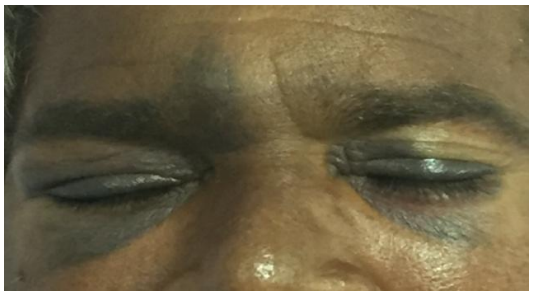


Fig. 3. Periorbital Ecchymosis

The case definition of dengue encephalitis includes fever, headache, reduced consciousness not explained by acute liver failure, shock, electrolyte derangement, or intracranial hemorrhage along with corroborating laboratory findings including detection of dengue virus or IgM in serum or CSF and neuroimaging suggestive of viral encephalitis [17].

The case discussed had clinical features consistent with encephalitis but was missed initially as no history of fever was given by the attendants accompanying the patient. In fact he was not accompanied by immediate family members. He was suspected to have a stroke in triage and NCCT brain as neuroimaging was done twice in 12 hours which was normal. MRI was not done as dengue viral encephalitis was not suspected. Later when he was diagnosed to have DF, MRI scan was refused by the family for financial reasons and CSF examination was not done in presence of severe thrombocytopenia. He was given 2 units of single donor platelets for qualitative as well as quantitative platelet deficiency and active bleeding. The case reported has absence of dengue IgM antibody in serum but dengue NS1 antigen was detected in the serum as he presented within 5-6 days of disease. It is known that neurological manifestations of dengue fever in absence of other features of systemic disease can present early during viremia. He was diagnosed to have dengue hemorrhagic fever-expanded dengue syndrome-dengue viral encephalitis.

4. CONCLUSION

1. Classical features of dengue fever may not always be present and neurological presentation is increasingly being recognized with increasing burden of DF globally. Clinicians should have a high index of suspicion for dengue encephalitis.
2. In absence of immediate family members accompanying a mentally obtunded patient MRI rather than CT scan may be a preferred mode of neuroimaging, even if stoke is suspected clinically.
3. Neurological manifestations can be life-threatening, and prevention of dengue is the only option available.
4. The disease is usually self-limiting and most patients make a good recovery if timely diagnosed and aggressively managed.

CONSENT

Written informed consent was obtained from the patient relatives for publication of this case report and all accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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