Case Report

Spontaneous intracranial hemorrhage associated with dengue fever: An emerging concern for general physicians

Abhijeet Singh[1], Viswesvaran Balasubramanian[2], Nitesh Gupta[2]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital,
[2]Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, New Delhi, India

Abstract

Dengue fever (DF) is an arboviral disease caused by a positive-sense RNA virus of the genus *Flavivirus*. The overall incidence of DF has increased exponentially worldwide over the last three decades. The atypical clinical manifestations of DF grouped under expanded dengue syndrome (EDS), have also been reported more frequently for the last decade. These unusual manifestations are usually associated with coinfections, comorbidities, or complications of prolonged shock. Intracranial hemorrhage (ICH) is one of the rare manifestations of the central nervous system involvement by dengue as a part of EDS. The pathogenesis and treatment of this manifestation also remain controversial. Therefore, we report a case of a previously healthy 65-year-old female who developed ICH as a part of EDS along with a brief review of literature.

Keywords: Dengue fever, expanded dengue syndrome, intracranial hemorrhage

Introduction

Dengue fever (DF), an arboviral illness, is caused by a positive-sense RNA virus of the genus *Flavivirus*.[1] The incidence of dengue has increased exponentially around the world over the last three decades.[2] The atypical or unusual manifestations recently grouped under expanded dengue syndrome (EDS) with neurological, hepatic, renal, and other isolated organ involvement, have also increased for the last decade. These manifestations are usually associated with coinfections, comorbidities, or complications of prolonged shock. Intracranial hemorrhage (ICH) is one of the rare manifestations of the central nervous system (CNS) involvement by dengue as a part of EDS. The pathogenesis is multifactorial attributed to the complex interplay of vasculopathy, coagulopathy, platelet dysfunction, and thrombocytopenia. There is a scarcity of knowledge on prevention and management of ICH secondary to DF. The role of prophylactic platelet transfusion and the need for elaborate assessment of hemostasis parameters remains uncertain. We are reporting a case of a previously healthy 65-year-old female who developed ICH as a part of EDS with a brief review of the literature.

Case Report

A 65-year-old previously healthy female was admitted to the hospital with chief complaints of high-grade fever, generalized body ache, and decreased appetite for 3 days, followed by breathlessness and altered sensorium for 2 days. Her vital parameters recorded on examination were pulse – 140/min, blood pressure – 90/60 mmHg, respiratory rate – 60/min, temperature 102°F, and pulse oximetry 60% on room air. She also had diffuse erythematous macular rash on the trunk and peripheral

Address for correspondence: Dr. Abhijeet Singh, Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi - 110 029, India.
E-mail: appu.abhijeet@gmail.com

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_56_18

How to cite this article: Singh A, Balasubramanian V, Gupta N. Spontaneous intracranial hemorrhage associated with dengue fever: An emerging concern for general physicians. J Family Med Prim Care 2018;7:618-28.

extremities. Neurological examination revealed Glasgow Coma Score (GCS) of 10 without any signs of meningeal irritation. Pupillary size and reaction were normal with bilateral extensors plantars. Other systemic examinations were unremarkable. She was found to have anemia (hemoglobin 8 g/dl), hematocrit 41%, and thrombocytopenia (90,000/cm^3) with normal total leukocyte count and coagulation profile. Dengue nonstructural (NS1) antigen (ELISA kit, PanBio Diagnostics, Brisbane, Australia) as well as IgM dengue antibody (Immunochromatographic kit, Standard Diagnostics Inc., Yongin, Korea) tests were detected positive in blood, whereas IgG antibody was negative. Serologies for malaria, chikungunya, leptospira, typhoid, and scrub typhus were negative. Rest all laboratory investigations were unremarkable. Her chest skiagram revealed bilateral infiltrates involving all zones suggestive of acute respiratory distress syndrome (ARDS). She was immediately placed on invasive mechanical ventilation in view of acute hypoxemic respiratory failure. The working diagnosis of ARDS secondary to dengue infection was established. Fluid resuscitation was started along with hemodynamic monitoring followed by subsequent resuscitation with vasopressor support. She was managed with ventilator strategy that comprised low tidal volume and high positive end-expiratory pressure settings with target fraction of inspired oxygen (FiO_2) ≤0.6 to maintain SaO_2 above 90%. On the 2nd day of hospital stay, her general condition further worsened as her GCS dropped to 5, bilateral pupils sluggishly reacting to light, and vasopressor requirement further increased. She also had two episodes of generalized tonic–clonic seizure. Serial platelet count was 65,000/cm^3. She was given one unit of packed red blood cells and six units of random donor platelets. Emergency noncontrast computed tomography revealed dilated bilateral lateral, third, and fourth ventricles showing hyperdense content of blood attenuation suggestive of intraventricular hemorrhage along with linear hyperdensities along bilateral sulcal spaces diffusely and along tentorium cerebelli as well as falx cerebrum suggestive of subarachnoid hemorrhage shown in Figure 1a-c. There was no midline shift. Fundus examination revealed no evidence of papilledema. Contrast magnetic resonance imaging including angiography excluded other sources of ICH, such as arteriovenous malformations, aneurysm, or dural fistulas. The patient was managed conservatively to maintain hemodynamic stability and repeat platelet transfusions were done. However, there was progressive deterioration and succumbed to death on the 3rd day of hospital stay.

Discussion

Dengue virus infection is a common mosquito vector-borne arboviral disease that may present with a varied spectrum of clinical manifestations. The infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), DF without hemorrhage or with unusual hemorrhage, dengue hemorrhagic fever (DHF) including shock known as dengue shock syndrome and EDS or isolated organopathy.[2] CNS involvement as a part of EDS continues to remain underrecognized and underreported. The various CNS manifestations include febrile seizures in young children, encephalopathy, encephalitis/aseptic meningitis, subdural effusions, mononeuropathies/polyneuropathies/Guillain–Barre Syndrome, and transverse myelitis.[1,2] These CNS manifestations are having pathogenetic mechanisms such as direct neurotrophic effects of virus, systemic manifestations of DF, and postinfectious immune complex-mediated mechanism. ICH, a potential life-threatening complication of dengue, is of uncommon occurrence in patients with severe dengue.[3] The incidence of dengue encephalopathy is estimated to range from 0.5% to 6.2%.[4-6] However, the incidence of ICH associated with DF is still uncertain. In a study by Cam *et al.*, of the 5400 patients with DF, only one had ICH.[4] There is a scarcity of data regarding the incidence, pathogenesis, and treatment modalities available to prevent and treat patients of dengue with ICH. A literature review of case reports as well as series describing demographic and clinical profile including the outcome of ICH in patients with DF are listed in Tables 1 and 2, respectively.[3,7-25] Presence of fever, reduced or altered consciousness, vomiting, seizures, and headache are common chief complaints in patients with ICH. The occurrence of ICH associated with DF can be localized or diffuse involving commonly cerebrum, ventricles, and less commonly cerebellum. Subdural, extradural, as well as subarachnoid hemorrhages were also reported. Various issues need to be considered in managing such complication of DF.

Platelet counts did not correlate with the incidence of ICH suggesting a complex interplay of multifactorial pathogenetic mechanisms for the occurrence of ICH.[3] The various postulated mechanisms include vasculopathy, coagulopathy,

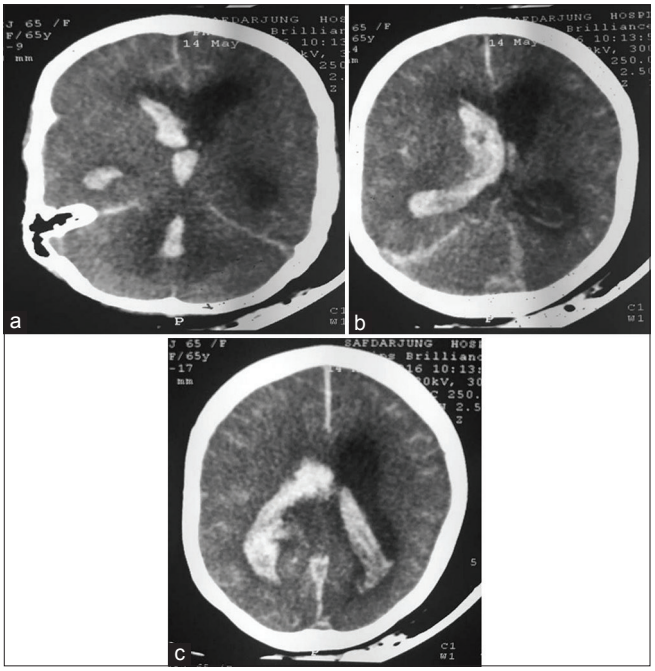

Figure 1: (a-c) Noncontrast computed tomography of head: Dilated bilateral lateral, third, and fourth ventricles showing hyperdense content of blood attenuation suggestive of intraventricular hemorrhage along with linear hyperdensities along bilateral sulcal spaces diffusely and along tentorium cerebelli as well as falx cerebrum suggestive of subarachnoid hemorrhage

Table 1: Demographic profile of cases of dengue fever associated intracranial hemorrhage from various case reports and series reported by different authors

Author	Years	Country	Number of cases	Age	Sex	Comorbid illness if any
Wafa *et al.*[7]	1999	Malaysia	1	19	Male	None, history of minor low-velocity vehicular accident
De Souza *et al.*[8]	2005	Brazil	1	21	Female	
Kumar *et al.*[9]	2007	India	1	68	Female	
Jensenius *et al.*[10]	2007	Norway	1	28	Female	
Kumar *et al.*[11]	2009	India	5	22	Male	
				15	Male	
				9	Male	
				40	Male	
				45	Female	
Wani *et al.*[12]	2010	Saudi Arabia	1	19	Female	
Mathew and Pandian[13]	2010	India	2	45	Female	
				35	Male	
Gera and George[14]	2010	India	1	27	Male	
Khanna *et al.*[15]	2011	India	1	28	Male	
Mittal and Jain[16]	2011	India	1	27	Female	
Assir *et al.*[17]	2012	Pakistan	1	20	Male	
Singh et al.[18]	2013	India	1	45	Male	
Singh *et al.*[19]	2013	India	1	40	Male	Leptospirosis
Vargas-Sánchez A[20]	2014	Mexico	1	64	Female	Hypertension
Singh *et al.*[21]	2015	India	2	45	Male	
				30	Male	
Nadarajah *et al.*[22]	2015	India	1	13	Female	
Sam *et al.*[3]	2016	Malaysia	9	47	Male	
				43	Male	DM, hypertension
				54	Male	
				59	Female	
				86	Male	DM, hypertension
				66	Male	Hypertension
				62	Male	
				69	Male	Hypertension
				48	Female	Hypertension
Jayasinghe *et al.*[23]	2016	Sri Lanka	1	24	Female	
Mehta [24]	2018	India	1	22	Male	
Sam [25]	2018	Malaysia	1	47	Male	
Current case	2018	India	1	65	Female	

DM: Diabetes mellitus

platelet dysfunction, and thrombocytopenia.[26] Detection of dengue IgM, IgG, and NS1 Ag in cerebrospinal fluid (CSF) of patients with dengue suggests breach of blood–brain barrier and blood–CSF barrier and vasculopathy secondary to immunopathological-related mechanisms.[27] Coagulopathy secondary to NS1 antigen-induced production of plasminogen cross-reactive antibodies leading to increased plasmin through plasminogen activation of fibrinolysis is also reported.[28] Thrombocytopenia and platelet dysfunction can be attributed to exhaustion from platelet activation triggered by immune complexes.[29] The lack of treatment guidelines for prevention and early recognition of ICH contributes to significant morbidity and mortality. High-risk population for EDS includes infants and the elderly, obesity, pregnant women, peptic ulcer disease, women who have menstruation or abnormal vaginal bleeding, hemolytic diseases such as glucose-6-phosphatase dehydrogenase deficiency, thalassemia and other hemoglobinopathies, congenital heart disease, chronic diseases such as diabetes mellitus, hypertension, asthma, ischemic heart disease, chronic renal failure, liver cirrhosis, and patients on steroid or nonsteroidal anti-inflammatory drug treatment.[2] Factors such as older patients, high baseline hematocrit levels, low platelet levels, prolonged APTT, female gender, vomiting, high absolute lymphocyte count, duration of shock, and high aspartate aminotransferase level are associated with severe bleeding in dengue patients.[30,31]

It is not possible to advise screening CT head in every patient with DF to detect ICH. CT should be considered only there is high index of suspicion based on clinical findings. Clinical experience from prior studies suggests that patients with secondary dengue infection identified by the detection of IgG early in the course of the disease with a positive NS1 antigen test and negative IgM are at higher risk of ICH carrying poor prognosis and should be monitored more closely with lower thresholds for diagnostic CT of the brain when suspicion of ICH is present.[3] In the present case report, though the patient was a female without

Table 2: Clinical profile of cases including the outcome of dengue fever associated intracranial hemorrhage from various case reports and series reported by different authors

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
Wafa *et al.*[7]	NS	3	Primary	160,000	30 (↓)	Deranged	Left frontal EDH and SDH with no MLS or e/o cerebral edema	IgM Ab + (detected twice)	No	NS	IV fluids, 4 units FFP and 3 units PRBC	Yes	Treated
De Souza *et al.*[8]	3	4	Primary	95,000	NS	Normal	Right pontine hematoma	IgM Ab +	Not initially but developed on the 6th day	ARDS Acute hepatitis AKI Right peripheral facial paralysis Hypoglycemia, hypokalemia	Vasopressor support, fluid resuscitation Hemodialysis	No	Treated under regular follow-up Difficulty in walking at 6 months
Kumar *et al.*[9]	NS	4	Primary	65,000	48.7 (↑)	Deranged ↑ PT and ↑ aPTT	Multiple focal parenchymal hemorrhages in the pons, right temporal lobe, left high frontal lobe and right parietal lobe with surrounding edema	IgM Ab + in blood and CSF	No	Hepatitis ↑ serum AST (985 U/l)	NS	No	Expired
Jensenius *et al.*[10]	2	8	Primary	189,000	NS	NS	Extensive SAH	Rapid test for serology negative IgM ELISA and IgG IFA Abs' +	No	Hepatitis Sr. LDH - 1950 U/l , AST- 272 U/l ALT - 121 U/l Splenomegaly	NS	NS	Expired within 6 h of admission
Kumar *et al.*[11]	2 in all cases	5	Primary in	39,000	NS	Deranged in all cases (↑PT)	Left basal ganglia hematoma	Serological confirmation in all cases	NS	NS	Yes (given to all cases) Platelet transfusion	No	Expired
		5	All cases	19,000			Right basal ganglia hematoma					No	Treated
		7		26,000			Left FT acute SDH					Yes	Treated

Contd...

Table 2: Contd...

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
		5		70,000			Right FP acute SDH					Yes	Treated
		15		15,000			Left basal ganglia hematoma					No	Expired
Wani *et al.*[12]	NS	3	Primary	21,000	52 (↑)	Normal	Right occipital hemorrhage with cerebral edema and MLS	ELISA NS1 antigen + IgM and IgG + RT-PCR +	NS	DHF, Petechial rash over extremities, Hepatitis, myositis	IV fluids Platelet and FFP transfusion IV Mannitol	No	Expired
Mathew and Pandian[13]	NS	7	Primary	75,000	NS	NS	Multiple hemorrhagic foci in the left parietal and temporal lobes	ELISA IgM Ab+in both cases	NS	DHF, plasma leakage, right-sided pleural effusion, ascites, cholelithiasis, Multiorgan involvement	Blood and platelet transfusion	No	Expired
	NS	3	Primary	30,000		NS	B/L cerebellar hemorrhages with edema, obstructive hydrocephalus, and multiple watershed infarcts		NA	NA	Symptomatic T/t	Yes	Treated mild gait ataxia with brisk deep tendon reflexes
Gera and George[14]	NS	5	Primary	19,000	32	NS	Thalamic and cerebellar hematoma with no midline extension	Ab raised	NA	Multiorgan involvement Encephalomyelitis	Steroids, symptomatic T/t	No	Treated
Khanna *et al.*[15]	NS	6	Primary	5000	NS	Normal	Right basal ganglia bleed with intraventricular extension	NS1+IgM Ab in blood and CSF both +	No	B/L pleural effusion Leukopenia Anemia	2 units PRBC 9 units platelet transfusion	No	Expired on the 10^{th} day of admission

Contd...

Table 2: Contd...

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
Mittal and Jain[16]	NS	7	Primary	100,000	24.3	Normal	B/L SDH not limited by suture lines over both cerebral hemispheres with focal petechial hemorrhage in left parietal region in subcortical white matter	IgM Ab +	No	Hepatitis Ascites Pleural effusion CSF showing lymphocytosis (10/mm3) and↑protein (173.7 mg/dl) Hypokalemia AMAN	IV fluids, phenytoin, Potassium chloride	No	Treated Walking with support After 1 month
Assir *et al.*[17]	NS	7	Primary	60,000	41.2-44	Normal	Right frontal lobe hematoma seen as a hyperdense lesion surrounded by a thin rim of hypodense area of edema with no MLS	IgM and IgG Abs' - during febrile phase IgM Ab+on day 10	No	Leukopenia initially followed by leukocytosis Hepatitis Subacute thyroiditis	Steroids Propranolol Head end elevation IV mannitol	No	Treated and discharged on 8th day of admission
Singh *et al.*[18]	NS	4	Primary	Low	NA	Normal	Medullary hematoma	IgM Ab +	No	Epidural hematoma T9-T11	Blood and platelet transfusions, spinal laminectomy with epidural hematoma evacuation	No	Expired
Singh *et al.*[19]	NS	5	Primary	38,000	39	Deranged	Left FP hematoma with mild perilesional edema without MLS	Dengue NS1+IgM Ab for Leptospira +	Not present at admission but developed subsequently	Hepatitis (total bilirubin 8.2 mg/dl, ALT 342 IU, AST 230 IU) AKI (creatinine 6.2 mg/dl, urea 108 mg/dl)	Fluids, Vasopressors, Tracheostomy, Blood transfusion Hemodialysis	No	Expired at 10th day of admission

Contd...

Table 2: Contd...

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
Vargas-Sánchez A[20]	NS	23	Primary	125,000	NS	Normal	Vermis and supravermis of Cerebellum, No ventricular extension	IgM Ab +	No	No	Conservative management	No	Treated Minimal cerebellar deficits
Singh *et al.*[21]	NS	9	Primary	17,000	40.2	Normal	Left frontal region hematoma	IgM Ab+in both cases	Not at admission but developed subsequently	No	IV fluids, antibiotics, antiepileptics and platelet transfusion	No	Treated
		13	Primary	20,000	33.4	Normal	Right FTP region SDH with SAH			Deranged LFT (? hepatitis)	Vasopressors in second case	No	Expired
Nadarajah *et al.*[22]	NS	3	Primary	35,000	NS	NS	Hemorrhages in B/L cerebral hemispheres including basal ganglia	IgM and IgG+in both blood and CSF	No	Mild B/L pleural effusion, free fluid in pelvis	IV steroids and Immunoglobulins	No	Treated with residual motor deficit in B/L lower limbs after 1 month
Jayasinghe *et al.*[23]	NS	6	Primary	40,000	At admission - 38 5^{th} day of fever - 46	Normal	Multiple SAH in right frontal, left parietal, and occipital lobes Right SDH and gross cerebral edema compressing B/L lateral ventricles, 3^{rd} ventricle and brainstem	IgM Ab +	No	Right pleural effusion, ascites, hypoalbuminemia (2.4 g/dl) Hepatitis Creatinine 49 micromol/l Central diabetes insipidus	IV steroids, Vitamin K, Tranexamic acid, Phenytoin, IV fluids Platelet and PRBC transfusion Intranasal Desmopressin	No	Expired

Contd...

Table 2: Contd...

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
Sam *et al.*[3]	NS	7	Secondary	31,000	42.7	Deranged	Right convexity SDH with MLS	NS1 antigen + for all cases except 2nd IgM + in 2nd and 3rd cases IgG + in 1st, 2nd and 7th cases	No	2nd case Hematemesis, Pleural effusion, Myocarditis, Hepatitis 4th case Gum bleeding 5th case Gum bleeding, hepatitis 7th case Hematemesis 9th case Ascites, pleural effusion	Platelet transfusion in all cases FFP also transfused in the first case Use of inotropes and vasopressors in case of shock	Yes	Expired
		6	Secondary	2000	41.7	Normal	Right basal ganglia hematoma with intraventricular extension and MLS		Yes			No	Expired
		7	Primary	15,000	43.1	Normal	Right convexity SDH with MLS		No			Yes	Expired
		9	Primary	3000	24.8	Normal	Right parietal SDH		No			No	Treated
		5	Primary	74,000	33	Normal	Left basal cistern SAH		No			No	Treated
		5	Primary	66,000	39.4	Normal	Frontal and left basal ganglia hematoma with generalized SAH and MLS		Yes			No	Expired
		6	Secondary	8000	34.1	Normal	Left convexity SDH with MLS		Yes			No	Expired
		4	Primary	17,000	32.4	Normal	Tentorium cerebelli SDH		No			No	Treated
		22	Primary	4000	43	Normal	Tentorium cerebelli SDH		No			No	Treated
Mehta *et al.*[24]	NS	8	Primary	40,000	NS	Normal	B/L symmetrical cerebellar hemorrhage with obstructive hydrocephalous	NS1 antigen +	NS	NS	6 units platelet transfusion	No	Treated
Sam *et al.*[25]	NS	7	Secondary	31,000	42.7	Deranged INR - 2.63 aPTT - 40.5 s	Left thalamic bleed Right FTP SDH with MLS and effacement of basal cisterns	NS1 antigen + IgM Ab - IgG Ab +	Not initially Occurred later	Hematemesis	FFP and platelet concentrate transfusion	Yes	Expired on the 3rd day of admission

Contd...

Table 2: Contd...

Author	Serotype	Day of detection of ICH from onset of symptoms	Primary or secondary infection	Platelet count at time of ICH (/ cm^3)	Hematocrit (%)	Coagulation Profile	Location of intracranial bleed on CT/ MRI brain	Dengue serological profile	Presence of shock	Associated complications	Medical intervention	Surgical intervention	Outcome/ neurological sequelae observed if any
Current case	NS	3	Primary	1st day - 90000 2nd day - 65,000	41	Normal	B/L lateral, 3rd and 4th ventricular hemorrhage and diffuse SAH along B/L sulcal spaces, tentorium cerebelli, and falx cerebrum	NS1 antigen + IgM Ab + IgG-	Yes	Anemia (8 g/dl) ARDS	6 units Platelet transfusion 1 unit PRBC Vasopressors IV fluids	No	Expired on the 3rd day of admission

(↓) means lower value than normal, (↑) means higher value than normal, Ab: Antibody; AKI: Acute Kidney Injury; aPTT: Activated partial thromboplastin time; ALT: Alanine transaminase; ARDS: Acute respiratory distress syndrome; AST: Aspartate transaminase; B/L: Bilateral; CSF: Cerebrospinal fluid; CT: Computed tomography; EDH: Extradural hemorrhage; ELISA: Enzyme-linked immunosorbent assay; FFP: Fresh-frozen plasma; FP: Frontoparietal; FT: Frontotemporal; FTP: Frontotemporoparietal; IFA: Immunofluorescence assay; INR: International normalized ratio; IV: Intravenous; LDH: Lactate dehydrogenase; LFT: Liver function test; MLS: Midline shift; MRI: Magnetic resonance imaging; PRBC: Packed red blood cells; PT: Prothrombin time; SDH: Subdural hemorrhage; SAH: Subarachnoid hemorrhage; T/t: Treatment; NS: Not specified, ICH: Intracranial hemorrhage; DHF: Dengue hemorrhagic fever; RT-PCR: Reverse transcriptase polymerase chain reaction; NA: Not available

any comorbidities, presence of risk factors of profound shock requiring vasopressor support, seizures, low platelet, and viremia, suggested by positive NS-1 antigen along with altered sensorium prompted early CT scan which revealed suggesting ICH.

The efficacy of platelet and fresh-frozen plasma transfusions for prevention of ICH and their role in the outcome of patients with ICH are controversial and debatable. The British Committee for Standardization in Haematology Guidelines and Directorate of National Vector Borne Diseases Control Programme, Government of India, recommend a trigger of 10,000/μl for platelet transfusion for stable thrombocytopenic patients without additional risk factors for bleeding.[32,33] These guidelines also recommend prophylactic platelet transfusions are not required in stable patients with platelet count below 20,000/μl. Studies have observed lack of benefit with prophylactic platelet transfusion. This has been attributed to lack of correlation between clinical bleed and platelet count indicating defects in alternate coagulation pathways, lack of sustained effect of platelet due to transient increment in platelet count with return to pretransfusion levels within 5 h of transfusion, risk of pulmonary edema, prolongation of hospitalization, and cost.[34-36] However, the role of prophylactic transfusion of platelets in the prevention of ICH remains contentious and debatable taking into consideration the significant morbidity and mortality associated with this rare event. In the present case, the patient was transfused 6 units of platelets. Despite that patient's intracranial bleed progressed and the patient succumbed. The role of other blood products such as fresh-frozen plasma, cryoprecipitate, and factor VIIa in prevention and treatment of ICH remain equally contentious and are generally administered by discretion of the physician taking into consideration the clinical condition of the patient.[37]

Since complex multifactorial pathogenic mechanisms are involved in bleeding manifestations of dengue, monitoring of platelet count and routine coagulation profile would not be sufficient, and a global assessment of efficiency of hemostatic mechanisms are warranted. Thromboelastography which involves rapid assessment of hemostatic clot stability based on the assessment of viscoelastic changes in clotting whole blood under low shear conditions after adding a specific coagulation activator might be helpful in determining a subset of dengue patients that may benefit from prophylactic transfusions to prevent life-threatening hemorrhages.[38] Other modalities such as thromboelastometry and platelet aggregometry may also aid in assessing the need for prophylactic transfusions. Although these studies are validated for goal-directed transfusion therapy in bleeding patients in major surgery and trauma and in bleeding hemophilic patients, their role in patients of dengue is unknown due to lack of clinical trials.[3]

Surgical management of dengue infection with ICH such as hematoma evacuation is often delayed and difficult as vasculopathy, coagulopathy and platelet dysfunction necessitate correction of platelets and other coagulation parameters with blood transfusions.[3] These factors may persist even after surgery.

Factors such as availability of neurosurgical centers, surgeons' experience, disease severity, comorbid illnesses, and distance for transportation of critically ill patients can affect the outcome. Neurosurgical procedures can be undertaken if platelets are above 100×10^9/L and international normalized ratio is maintained from 1.5 to 1.7.[38-40] Timely surgical intervention if performed within 8 h of hemorrhage was associated with improved outcome.[41,42] These recommendations need to be validated for ICH associated with dengue infection. However, in the present case, deteriorated rapidly before decision for surgery could be undertaken and finally succumbed to death on the 3rd day of illness indicating fulminant course of illness.

The expanding literature regarding incidence and outcome of DF associated with atypical CNS manifestations such as ICH predicts high morbidity and mortality. It is very difficult and even challenging for general physicians to take action even if diagnosed early as there is still uncertainty in management. This warrants health-care delivery systems to revise existing guidelines and frame strict protocols for managing such complications to reduce morbidity as mortality worldwide.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control- New Edition. (WHO/HTM/NTD/DEN/2009.1). Geneva: World Health Organization; 2009. Available from: http://www.who.int/rpc/guidelines/9789241547871/. [Last accessed on 2017 Nov 28].
2. World Health Organization. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Revised and Expanded Edition. Regional Office for South-East Asia: WHO; 2011. Available from: http://www.apps.who.int/iris/bitstream/10665/204894/1/B4751.pdf. [Last accessed on 2017 Nov 28].
3. Sam JE, Gee TS, Nasser AW. Deadly intracranial bleed in patients with dengue fever: A series of nine patients and review of literature. J Neurosci Rural Pract 2016;7:423-34.
4. Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, Heegaard ED, *et al.* Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg 2001;65:848-51.
5. Hendarto SK, Hadinegoro SR. Dengue encephalopathy. Acta Paediatr Jpn 1992;34:350-7.
6. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, *et al.* Neurological manifestations of dengue infection. Lancet 2000;355:1053-9.
7. Wafa SR, Jamsari S, Karis BM. A case report: Intracranial haemorrhage in a patient with probable dengue fever. Med J Malaysia 1999;54:273-6.
8. de Souza LJ, Martins AL, Paravidini PC, Nogueira RM, Gicovate Neto C, Bastos DA, *et al.* Hemorrhagic encephalopathy in dengue shock syndrome: A case report. Braz J Infect Dis 2005;9:257-61.
9. Kumar J, Kumar A, Gupta S, Jain D. Dengue hemorrhagic fever: An unusual cause of intracranial hemorrhage. J Neurol Neurosurg Psychiatry 2007;78:253.
10. Jensenius M, Berild D, Ormaasen V, Maehlen J, Lindegren G, Falk KI, *et al.* Fatal subarachnoidal haemorrhage in a Norwegian traveller with dengue virus infection. Scand J Infect Dis 2007;39:272-4.
11. Kumar R, Prakash O, Sharma BS. Intracranial hemorrhage in dengue fever: Management and outcome: A series of 5 cases and review of literature. Surg Neurol 2009;72:429-33.
12. Wani AM, Mejally MA, Hussain WM, Maimani WA, Hanif S, Khoujah AM, *et al.* Skin rash, headache and abnormal behaviour: Unusual presentation of intracranial haemorrhage in dengue fever. BMJ Case Rep 2010;2010. pii: bcr06.2009.1949.
13. Mathew S, Pandian JD. Stroke in patients with dengue. J Stroke Cerebrovasc Dis 2010;19:253-6.
14. Gera C, George U. Acute disseminating encephalomyelitis with hemorrhage following dengue. Neurol India 2010;58:595-6.
15. Khanna A, Atam V, Gupta A. A case of dengue encephalitis with intracerebral hemorrhage. J Glob Infect Dis 2011;3:206-20.
16. Mittal M, Jain N. Subdural haematoma and axonal polyneuropathy complicating dengue fever. BMJ Case Rep 2011;2011. pii: bcr1220103672.
17. Assir MZ, Jawa A, Ahmed HI. Expanded dengue syndrome: Subacute thyroiditis and intracerebral hemorrhage. BMC Infect Dis 2012;12:240.
18. Singh M, Garg K, Bisht A, Sharma BS, Singh PK, Pandia M, *et al.* Spinal epidural hematoma with myelitis and brainstem hemorrhage: An unusual complication of dengue fever. Neurol India 2013;61:541-3.
19. Singh RK, Ghatak T, Baronia AK, Garg P. Intracranial hemorrhage in a patient coinfected with dengue and leptospirosis. J Neurosci Rural Pract 2013;4:366-7.
20. Vargas-Sánchez A, Chiquete E, Gutiérrez-Plascencia P, Castañeda-Moreno V, Alfaro-Castellanos D, Paredes-Casillas P, *et al.* Cerebellar hemorrhage in a patient during the convalescent phase of dengue fever. J Stroke 2014;16:202-4.
21. Singh J, Dinkar A, Atam V, Misra R, Kumar S, Gupta KK, Patel ML. Intracranial hemorrhage in dengue fever: A case series. JMSCR 2015;3:4447-52.
22. Nadarajah J, Madhusudhan KS, Yadav AK, Gupta AK, Vikram NK. Acute hemorrhagic encephalitis: An unusual presentation of dengue viral infection. Indian J Radiol Imaging 2015;25:52-5.
23. Jayasinghe NS, Thalagala E, Wattegama M, Thirumavalavan K. Dengue fever with diffuse cerebral hemorrhages, subdural

hematoma and cranial diabetes insipidus. BMC Res Notes 2016;9:265.

24. Mehta M, Sharma PK, Garg RK. An uncommon complication of dengue. J Stroke Cerebrovasc Dis 2018;27:e46-7.
25. Sam JE, Gee TS, Wahab NA. Fatal intracranial hemorrhage in a patient with severe dengue fever. Asian J Neurosurg 2018;13:56-8.
26. Chuansumrit A, Tangnararatchakit K. Pathophysiology and management of dengue hemorrhagic fever. Transfus Altern Transfus Med 2006;8:3-11.
27. Puccioni-Sohler M, Rosadas C, Cabral-Castro MJ. Neurological complications in dengue infection: A review for clinical practice. Arq Neuropsiquiatr 2013;71:667-71.
28. Chuang YC, Lin J, Lin YS, Wang S, Yeh TM. Dengue virus nonstructural protein 1-induced antibodies cross-react with human plasminogen and enhance its activation. J Immunol 2016;196:1218-26.
29. Boonpucknavig S, Vuttiviroj O, Bunnag C, Bhamarapravati N, Nimmanitya S. Demonstration of dengue antibody complexes on the surface of platelets from patients with dengue hemorrhagic fever. Am J Trop Med Hyg 1979;28:881-4.
30. Tee HP, How SH, Jamalludin AR, Safhan MN, Sapian MM, Kuan YC, *et al.* Risk factors associated with development of dengue haemorrhagic fever or dengue shock syndrome in adults in hospital Tengku Ampuan Afzan Kuantan. Med J Malaysia 2009;64:316-20.
31. Chamnanchanunt S, Kanagaraj D, Thanachartwet V, Desakorn V, Rojnuckarin P. Early predictors of clinically significant bleeding in adults with dengue infection. Southeast Asian J Trop Med Public Health 2012;43:890-9.
32. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol 2003;122:10-23.
33. Dutta AK, Biswas A, Baruah K, Dhariwal AC. National guidelines for diagnosis and management of dengue fever/dengue haemorrhagic fever and dengue shock syndrome. J Indian Med Assoc 2011;109:30-5.
34. Chaudhary R, Khetan D, Sinha S, Sinha P, Sonker A, Pandey P, *et al.* Transfusion support to dengue patients in a hospital based blood transfusion service in North India. Transfus Apher Sci 2006;35:239-44.
35. Stanworth SJ, Dyer C, Choo L, Bakrania L, Copplestone A, Llewelyn C, *et al.* Do all patients with hematologic malignancies and severe thrombocytopenia need prophylactic platelet transfusions? Background, rationale, and design of a clinical trial (trial of platelet prophylaxis) to assess the effectiveness of prophylactic platelet transfusions. Transfus Med Rev 2010;24:163-71.
36. Lum LC, Abdel-Latif Mel-A, Goh AY, Chan PW, Lam SK. Preventive transfusion in dengue shock syndrome-is it necessary? J Pediatr 2003;143:682-4.
37. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. Transfus Med Rev 2012;26:1-3.
38. Chan KH, Mann KS, Chan TK. The significance of thrombocytopenia in the development of postoperative intracranial hematoma. J Neurosurg 1989;71:38-41.
39. Matevosyan K, Madden C, Barnett SL, Beshay JE, Rutherford C, Sarode R, *et al.* Coagulation factor levels in neurosurgical patients with mild prolongation of prothrombin time: Effect on plasma transfusion therapy. J Neurosurg 2011;114:3-7.
40. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: When to transfuse. Hematology Am Soc Hematol Educ Program 2013;2013:638-44.
41. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, *et al.* Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): A randomised trial. Lancet 2013;382:397-408.
42. Gregson BA, Broderick JP, Auer LM, Batjer H, Chen XC, Juvela S, *et al.* Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. Stroke 2012;43:1496-504.