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

Abhijeet Singh1, Viswesvaran Balasubramanian2, Nitesh Gupta2

1Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, 2Department 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. The incidence of dengue has increased exponentially around the world over the last three decades. The atypical clinical manifestations of DF 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 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...
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/cm³) 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 skigram 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 (FiO₂) ≤0.6 to maintain SaO₂ 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/cm³. 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 falk 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.[3] 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.[6,8] 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%.[8,9] 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.[10] 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.[17,25] 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,
platelet dysfunction, and thrombocytopenia.[20] 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

| 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  |                                          |
| Wani et al.[12] | 2010  | Saudi Arabia | 1           | 19  | Female |                                          |
| Mathew and Pandian[13] | 2010 | India | 2               | 45  | Female |                                          |
| 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 |                                          |
| Assil 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  |                                          |
| Nadarajah et al.[22] | 2015 | India | 1               | 13  | Female |                                          |
| Sam et al.[23]  | 2016  | Malaysia   | 9               | 47  | Male  | DM, hypertension                       |
| Jayasinghe et al.[24] | 2016 | Sri Lanka | 1               | 24  | Female |                                          |
| Mehta[25]       | 2018  | India      | 1               | 22  | Male  |                                          |
| Sam[23]         | 2018  | Malaysia   | 1               | 47  | Male  |                                          |
| Current case    | 2018  | India      | 1               | 65  | Female |                                          |

DM: Diabetes mellitus
### 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 (/ cm³) | 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.⁷ⁱ           | 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.⁸⁵       | 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.⁹¹          | NS       | 4                                             | Primary                        | 65,000                               | 48.7 (↑)       | Deranged            | 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.¹⁰⁵      | 2        | 8                                             | Primary                        | 189,000                              | NS             | NS                  | Extensive SAH                                             | Rapid test for serology negative IgM ELISA and IgG IFA Abs’ + Serological confirmation in all cases | 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.¹¹¹          | 2 in all cases | 5                                 | Primary in                     | 39,000                               | NS             | Deranged in all cases (↑PT) | Left basal ganglia hematoma                                 | NS                        | Yes (given to all cases) Platelet transfusion | Yes                     | No                  | Expired           |
|                          |          | 5                                             | All cases                      | 19,000                               |                |                    | Left FT acute SDH                                           |                           |                  |                            |                                      | No                  | Treated           |
|                          |          | 7                                             |                                | 26,000                               |                |                    | Left FT acute SDH                                           |                           |                  |                            |                                      | Yes                 | Treated           |

*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 |
|------------------------|----------|-----------------------------------------------|---------------------------------|------------------------------------------|----------------|---------------------|-----------------------------------------------|-----------------------------|-----------------|------------------------|-------------------|---------------------|------------------------|
| Singh et al.           | NS       | 5                                             | Primary                         | 70,000                                    | Right FP acute SDH | Left basal ganglia hematoma | 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                |
| Wani et al. [12]       | NS       | 3                                             | Primary                         | 21,000                                    | 52 (↑) Normal | Right occipital hemorrhage with cerebral edema and MLS | Multiple hemorrhagic foci in the left parietal and temporal lobes | ELISA IgM Ab+ in both cases | NS | No | Expired                |
| Mathew and Pandian [13]| NS       | 7                                             | Primary                         | 75,000                                    | NS Normal | Right basal ganglia bleed with intraventricular extension | B/L cerebellar hemorrhages with edema, obstructive hydrocephalus, and multiple watershed infarcts | NS1 + IgM Ab in blood and CSF both + | 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 | 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                                      | Normal     | Right basal ganglia bleed with intraventricular extension | 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 10th day of admission |

Contd...
| Author                | Serotype | Day of detection of ICH from onset of symptoms | Platelet count at time of ICH (\(\times 10^3\)) | 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                                             | 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              | IV fluids, phenytoin, Potassium chloride | No                                      | Treated Walking with support After 1 month |
| Assir et al [17]     | NS       | 7                                             | 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 | Leukopenia initially followed by leukocytosis | Steroids, Propranolol, Head end elevation | No                                      | Treated and discharged on 8th day of admission |
| Singh et al [18]     | NS       | 4                                             | Low                                           | NA             | Normal              | Medullary hematoma                               | IgM Ab +                  | No              | Epileptic status       | Blood and platelet transfusions, spinal laminectomy | No                                      | Expired                                      |
| Singh et al [19]     | NS       | 5                                             | 38,000                                        | 39             | Deranged            | Left FP hematoma with mild perilesional edema without MLS | Dengue NS1+IgM Ab for Leptospiro + | Not present at admission but developed subsequently | Hepatitis (total bilirubin 8.2 mg/dl, ALT 342 IU, AST 230 IU) | Fluids, Vasopressors, Tracheostomy, Blood transfusion | No                                      | Expired at 10th day of admission                  |
### Table 2: Contd...

| Author       | Serotype | Day of detection of ICH from onset of symptoms | Primary or secondary infection | Platelet count at time of ICH (× 10⁵/cm²) | 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 et al. [20] | NS       | 23  | Primary  | 125,000 | NS | Normal | Vermis and supravermis of Cerebellum, No ventricular extension | IgM Ab+ in both cases | No | No | Conservative management | No | 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 | No | Not at admission but developed subsequently | IV fluids, antibiotics, antiepileptics and platelet transfusion | No | Treated |
| 13            | Primary  | 20,000 | 33.4 | Normal | Right FTP region SDH with SAH | 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 | Expired |
| Nadarajah et al. [22] | NS       | 3   | Primary  | 35,000 | NS | NS | Hemorrhages in B/L cerebral hemispheres including basal ganglia | IgM Ab+ in both blood and CSF | 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 | Treated with residual motor deficit in B/L lower limbs after 1 month | Expired |
| Jayasinghe et al. [23] | NS       | 6   | Primary  | 40,000 | At admission - 38 5th 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, 3rd 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, Platelet and PRBC transfusion Intranasal Desmopressin | No | Treated with residual motor deficit in B/L lower limbs after 1 month | Expired |

Contd...
Table 2: Contd...

| Author          | Serotype | Day of detection of ICH from onset of symptoms | Platelet count at time of ICH (× per cm²) | 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[23]   | NS       | 7                                             | 31,000                                    | 42.7           | Deranged            | Right convexity SDH with MLS                      | NS1 antigen + for all cases except 2nd, 3rd, and 7th cases | No                | 2nd case Hematemesis, Pleural effusion, Myocarditis, Hepatitis | Platelet transfusion in all cases FFP also transfused in the first case | Yes                 | Expired                                      |
| 6               | Secondary| 2000                                          | 41.7                                      | Normal         |                     | Right basal ganglia hematoma with intraventricular extension and MLS | IgG + in 1st, 2nd and 3rd cases | Yes              |           | 4th case Gum bleeding | No                    | No                  | Expired                                      |
| 7               | Primary  | 15,000                                        | 43.1                                      | Normal         |                     | Right convexity SDH with MLS                      | No                         | No                |           | 5th case Gum bleeding, hepatitis         | No                    | No                  | Expired                                      |
| 9               | Primary  | 3000                                          | 24.8                                      | Normal         |                     | Right parietal SDH                                | No                         | No                |           | 7th case Hematemesis | No                    | No                  | Expired                                      |
| 5               | Primary  | 74,000                                        | 33                                        | Normal         |                     | Left basal cistern SAH                            | No                         | No                |           | 9th case Ascites, pleural effusion | No                    | No                  | Expired                                      |
| 5               | Primary  | 66,000                                        | 39.4                                      | Normal         |                     | Frontal and left basal ganglia hematoma with generalized SAH and MLS | Yes                        | Yes               |           |                      | Yes                  | No                  | Expired                                      |
| 6               | Secondary| 8000                                          | 34.1                                      | Normal         |                     | Left convexity SDH with MLS                       | Yes                        | No                |           |                      | No                    | No                  | Expired                                      |
| 4               | Primary  | 17,000                                        | 32.4                                      | Normal         |                     | Tentorium cerebelli SDH                           | No                         | No                |           |                      | No                    | No                  | Expired                                      |
| 22              | Primary  | 4000                                          | 43                                        | Normal         |                     | Tentorium cerebelli SDH                           | No                         | No                |           |                      | No                    | No                  | Expired                                      |
| Mehta et al[24] | NS       | 8                                             | 40,000                                    | NS             | Normal              | B/L symmetrical cerebellar hemorrhage with obstructive hydrocephalus | NS1 antigen +               | No                |           |                      | No                    | No                  | Expired                                      |
| Sam et al[23]   | NS       | 7                                             | 31,000                                    | 42.7           | Deranged            | Left thalamic bleed                               | NS1 antigen + for all cases except 2nd, 3rd, and 7th cases | No                | 2nd case Hematemesis, Pleural effusion, Myocarditis, Hepatitis | Platelet transfusion in all cases FFP also transfused in the first case | Yes                 | Expired on the 3rd day of admission |
|                 |          |                                               |                                           |                |                     | Right FTP SDH with MLS and effacement of basal cisterns | IgM Ab - IgG Ab +          | Not initially occurred |                      | Hematemesis and FFP and platelet concentrate transfusion | Yes                  | No                  | Expired                                      |
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.[39]

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.[39] 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 $10^9/L$ and international normalized ratio is maintained from 1.5 to 1.7.\textsuperscript{18-20} Timely surgical intervention if performed within 8 h of hemorrhage was associated with improved outcome.\textsuperscript{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.

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**Conflicts of interest**

There are no conflicts of interest.

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