

## Original Article

# Retrospective analysis of prognostic factors in dengue infected patients with intracranial bleed

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## Abstract

**Background:** Dengue is one of the most common mosquito-transmitted arboviral disease of tropical and a few subtropical areas in the world. It is estimated that approximately 100 million cases occur per year and approximately 2.5 billion people are at risk of developing dengue infection. Hemorrhagic complications causing encephalopathy are quite rare but fatal consequences of this deadly disease. This study was conducted to discuss the prognostic factors in the management of intracranial hemorrhage in dengue infected patients.

**Methods:** This retrospective study was conducted in the neurosurgery department of our tertiary healthcare centre. Duration of the study was 1 year, and 18 patients who presented with intracranial bleed and required neurosurgical care were included in this study. All patients had deranged coagulation profile and were thrombocytopenic. All the patients were given platelet concentrates for correction of thrombocytopenia. Eight of these patients had deterioration in their neurological status, and 6 of them underwent surgery.

**Results:** Out of 18 patients, 12 (66.66%) were managed conservatively, including one case of cervical extradural hemorrhage. Five patients who were conservatively managed died because they had deep-seated bleed and rapid deterioration. The remaining 7 patients who were managed conservatively improved well with few residual deficits. Six (33.33%) patients who underwent surgery had excellent outcome with one case of mortality.

**Conclusion:** Very high index of suspicion is required in dengue infected patients for neurological complications, especially during the convalescence period. Special attention should be given to those patients who have altered sensorium, and should not be misinterpreted as fever delirium or toxic encephalopathy. It requires immediate attention and further neurological investigation (including thorough clinical examination). Timely diagnosis using a computed tomography scan and early neurosurgical intervention after rapid correction of thrombocytopenia can save many lives.

**Key Words:** Dengue hemorrhagic fever, extradural hematoma, intracranial bleed, subdural hematoma, thrombocytopenia

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## INTRODUCTION

Dengue is a mosquito-borne infection transmitted to humans by *Aedes aegypti* and caused by one of the four closely related virus serotypes of the genus *Flavivirus*, family *Flaviviridae*.<sup>[5,7]</sup> The global prevalence of dengue has grown dramatically in recent years, and it has become endemic in different parts of the world.<sup>[5,7]</sup> Dengue fever and dengue hemorrhagic fever (DHF) are acute febrile diseases found in the tropics with a geographic distribution similar to malaria.<sup>[13]</sup> Encephalopathy is a quite rare but fatal complication of dengue virus infection. The treatment of DHF with central nervous system (CNS) involvement is supportive and symptomatic and rarely requires surgical intervention.<sup>[15]</sup> We report this uncommon complication of dengue in a series of 18 dengue patients who presented with brain hemorrhage out of a total 238 dengue serology positive patients with neurological symptoms, who were admitted in a single hospital, and discuss their management and outcome.

## MATERIALS AND METHODS

We collected retrospective data from dengue infected patients with neurological manifestations in our tertiary health centre, i.e., Government medical college, Kota (Rajasthan), India from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2015 [Figures 1-3].

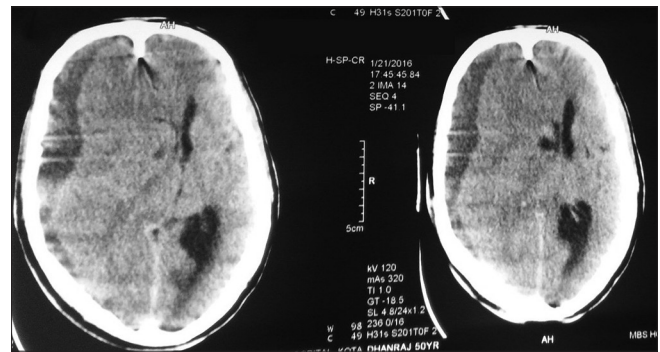
## RESULTS

Table 1 shows the details of dengue infected patients and their complications while their demographic details, presenting diagnosis, and surgical outcomes are elaborated in Table 2. All the patients who were included in this study had no predisposing factor for intracranial bleed such as head injury, hypertension, or previously known coagulopathy before this episode of illness.

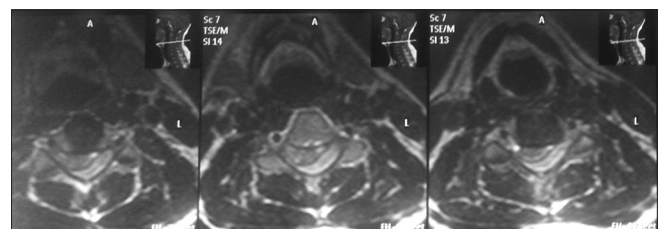
**Table 1: Details of dengue infected patients and complications**

Characteristics	Numbers	Percentage
Total serologically confirmed cases	1627	100%
Dengue fever	318	19.54%
Dengue Haemorrhagic Fever (DHF)	292	17.94%
Dengue Shock Syndrome (DSS)	37	2.27%
Neurologically affected cases	238	14.62%
Direct Neurotropic complications like encephalitis, myositis	41	2.51%
Systemic Neurological complications like stroke, venous sinus thrombosis, optic neuritis, myelitis, intracranial bleed etc	197	12.10%
Total cases of Intracranial bleed	18	1.1%
Neurosurgical intervention required	6	0.37%

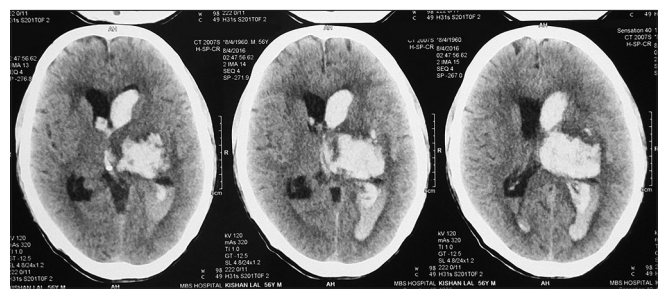
All of them had typical neurological clinical presentations such as headache, altered consciousness, and limb weakness with deranged coagulation profile and thrombocytopenia. All were confirmed serologically for dengue viral infection. All patients were young adults and had intracranial bleed around convalescence (1 week after the onset of fever). All patients had moderate-to-severe headache before neurological deterioration. Only two of them had a history of nasal bleed and petechiae. All the patients were given platelet concentrate transfusions to keep platelet count above 100000/mL and blood components were made available during the perioperative period. Adequate hydration was maintained according to urine output and clinical assessment perioperatively in all patients, and cerebral decongestants were used according to the need. Scalp block with intravenous dexmedetomidine infusion was used in two patients for chronic subdural hemorrhage surgery while rest of them were managed with balanced general anaesthesia with mechanical ventilation. Short acting anaesthetic



**Figure 1: NCCT of the head showing right frontotemporoparietal acute on chronic SDH**



**Figure 2: MRI of the cervical spine showing epidural haematoma with cord compression**



**Figure 3: NCCT of the head showing left thalamic ICH with intraventricular extension**

**Table 2: Demographic details of the enrolled dengue infected patients with neurological manifestations**

Age/ Sex	Serology	Platelet Counts	GCS Score	Radiological diagnosis	Management	Anesthesia	Outcome
37/M	Type-2	40700	E3V5M5	EDH	Craniotomy and hematoma evacuation	GA	Discharged
50/M	Type-2	55000	E3V4M3	EDH	Craniotomy and hematoma evacuation	GA	Discharged
25/M	Type-2	25700	E3V5M4	Acute SDH	Craniotomy and hematoma evacuation	GA	Discharged
50/M	Type-2	35000	E3V4M3	Chronic SDH Figure 1	Burr hole and hematoma evacuation	Scalp block with sedation	Discharged
22/F	Type-2	49000	E3V4M4	EDH	Conservative		Discharged
38/M	Type-2	22000	E4V4M6	ICH	Conservative		Discharged
29/M	Type-2	36000	E4V4M5	SDH	Conservative		Discharged
43/F	Type-2	42000	E3 V4M5	ICH	Conservative		Discharged
64/F	Type-2	38000	E3V4M6	ICH	Conservative		Discharged
14/M	Type-2	18000	E1V2M3	ICH	Craniotomy and hematoma evacuation	GA	Died
42/M	Type-2	64000	E3V2M4	ICH	Conservative		Discharged
23/M	Type-2	35000	E3V3M4	SDH	Conservative		Discharged
33/F	Type-2	40000	E4V3M5	ICH	Conservative		Discharged
16/M	Type-2	34600	E4V4M6	ICH	Conservative		Discharged
28/F	Type-2	45800	E2V2M1	Brain stem bleed	Conservative		Died
44/M	Type-2	25200	E3V5M4	Chronic SDH	Burr hole & hematoma evacuation	Scalp block with sedation	Discharged
61/M	Type-2	30000	E1V1M1	ICH Figure 3	Conservative		Died
37/F	Type-2	42000	E3V5M3	Cervical EDH Figure 2	Conservative		Discharged

drugs were used and general anaesthesia was maintained with oxygen, isoflurane and vecuronium. All operated patients were extubated immediately in the postoperative period and shifted to neurosurgery ICU with stable hemodynamics.

After detailed observation of all these cases, we conclude that Glasgow coma scale (GOS) scores of >9, early admission, early serological and radiological diagnosis, early effective intravenous fluid therapy, anti-edema agents and platelet transfusion, and early neurosurgical interventions in needy patients under balanced anaesthesia are good prognostic indicators. In contrast, deep seated intracerebral massive hemorrhage, delay in effective management, associated severe meningoencephalitis, and old age of patients with associated comorbidities are bad prognostic criteria.

## DISCUSSION

It is estimated that every year there are 100 million cases of dengue fever and 2.5 billion people at risk. Dengue is the second most important mosquito-borne disease affecting humans after malaria.<sup>[13]</sup> Dengue fever is endemic in some parts of India.<sup>[9]</sup> There are increase in dengue cases after the monsoon (rainy season) when the conditions are ideal for mosquito breeding, that is, hot and humid environment with water pooling. Primary prevention of dengue mainly includes eliminating or reducing the mosquito vector for dengue.<sup>[4]</sup> In medical colleges and attached hospitals situated in the south-east part of Rajasthan, India, with easy access to emergency care, quality care, and a policy of hospitalizing patients

with any clinical, biological, or social warning sign, approximately 15% of the patients seen for dengue fever had central nervous system dysfunction mostly around the 5<sup>th</sup> or 6<sup>th</sup> day of fever. We found approximately 1.1% cases of intracranial or neurological bleed in imaging from 1627 dengue infected patients, whereas 0.37% patients underwent neurosurgical intervention among all dengue positive patients. Most patients did not undergo cerebrospinal fluid examination because thrombocytopenia was assumed to make the spinal tap risky.

Dengue is a mosquito-borne infection caused by an arbovirus. This disease is caused by any one of the 4 types of viruses, namely, dengue 1, 2, 3, and 4. People can be infected by one or more types during one episode of illness, but only once by the same type in their entire life time. Dengue 1 causes high fever and joint pains, dengue 2 causes hemorrhagic fever resulting in spontaneous bleeding from skin and gums, dengue 3 causes high fever, whereas dengue 4 causes DHF with shock. Each serotype is different from each other and there is no cross-protection. Epidemics can be caused by multiple serotypes.<sup>[10]</sup> The diagnosis of dengue is usually made clinically. According to the World Health Organization definition, DHF is diagnosed when all the 4 criteria are fulfilled. These are fever, hemorrhagic tendencies (positive tourniquet test, spontaneous bruising, bleeding from mucosa, gingiva, hematemesis, bleeding from injection sites etc), thrombocytopenia (<100,000 platelets/mm<sup>3</sup> or estimated as <3 platelets per high-power field), and evidence of plasma leakage (hematocrit 20% higher than expected or drop in hematocrit of 20% or more from baseline after intravenous fluid administration).<sup>[12]</sup> Although common

complications of dengue fever are fatigue and tiredness, DHF is the most dangerous of all. This can lead to bleeding and shock. The incidence of CNS involvement in dengue infection is low and ranges from 0.88% to 10%; the fatality rate is high. This encephalopathy may occur as a consequence of microcapillary hemorrhage leading to intracranial bleed, cerebral edema, hyponatremia, cerebral anoxia, and release of toxic products. Cardiac disturbances and reactive hepatitis have been reported during recent years.<sup>[2]</sup>

The most critical phase of this viral infection is the defervescent phase when the fever subsides but the patient develops life-threatening thrombocytopenia due to complement activation by viral antigens binding to platelets. The mainstay of treatment is supportive therapy. Platelet transfusion is rarely indicated unless the platelet level drops significantly or if there is significant bleeding. However, the transfusion is recommended on platelet count falling below 20000/ml even without hemorrhage or approximately 50000/ml with hemorrhage. Surgical intervention for ocular and intracranial surgeries can be undertaken after correction of coagulation defect with platelet count above 100000/mL.<sup>[1]</sup> The most common hemorrhagic tendencies described in the literature are petechial hemorrhage, ecchymosis, gastrointestinal bleed, epistaxis, and others, however, in our cases, there was only history of nasal bleed, and petechiae were present only in 2 cases.<sup>[6]</sup> This raises the concern whether CNS is more prone to bleed than other sites. Altered sensorium in these patients may be incorrectly attributed to shock, delirium, and fever. Any delay in the diagnosis of intracranial bleed in these patients may be fatal. Urgent and timely operative intervention in five cases led to good recovery in spite of poor neurologic status before surgery and one patient died because of poor preoperative status with large intracerebral bleed.

The exact mechanism of bleeding in DHF is not clear, however, it appears to be multifactorial. Thrombocytopenia, prolonged prothrombin time, mild degree of disseminated intravascular coagulation, and hepatic dysfunction all seem to contribute synergistically. Recent data do not advocate a delay in extubating patients when neurological impairment is the only reason for prolonged intubation. An appropriate choice of sedatives and analgesics during mechanical ventilation of neurosurgical patients allows for a narrower range of wake-up time, and weaning protocols incorporating respiratory and neurological measures may improve outcome. Shivbalan *et al.*<sup>[11]</sup> observed that spontaneous bleed was most commonly associated with deranged prothrombin time. A combination of (a) biphasic pattern of fever, (b) hemo-concentration, (c) platelet count less than 50000/mm<sup>3</sup>, and (d) elevated ALT had a sensitivity of 79.2%, specificity of 64.7% with a positive predictive value of 70%, and a negative predictive value of 75% in predicting spontaneous bleeding in

dengue.<sup>[3]</sup> Tripathi *et al.*<sup>[14]</sup> observed hemorrhage in 2.5% of cases in their series. This included complications such as hematemesis (28%), epistaxis (27%), malena (14%), lymphadenopathy, especially cervical (31%), palatal rashes (27%), and hepatomegaly (24%); however, none had intracranial bleed. None of the patients in our series had such findings except major intracranial bleed. Initial GCS score and the existence of systemic complications were strong predictive factors for prognosis of ICH. Calculated hematoma volume also had predictive value for clinical outcomes.<sup>[8]</sup>

This is the first large longitudinal study to provide incidence rates for CNS signs during dengue fever among patients seen at a tertiary health care centre in our zone. Overall, the present study suggests that neurological signs of dengue are not exceptional even in patients without the most severe features of dengue. These manifestations were spontaneously resolute and were associated with patients' various allergic or hemorrhagic manifestations.

## CONCLUSION

GCS scores (>9), early serological and radiological diagnosis, early effective intravenous fluid supportive therapy, anti-edema agents and platelets transfusions, and obviously early neurosurgical interventions in needy patients under balanced anesthesia are good prognostic indicators in such patients. A high degree of suspicion in dengue is required, especially during convalescence in patients who are disoriented and have altered sensorium. It should not be misinterpreted as fever delirium or toxic encephalopathy. It needs immediate attention and CT scan. Timely diagnosis, adequate fluid management, and intervention can save many precious lives.

## Disclosure

There is no conflict of interest for this study. Institutional ethical approval was taken for this research.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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