

Spontaneous subdural hematoma and diabetes insipidus in severe dengue in a south-eastern Caribbean island: case report and review of literature

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ABSTRACT

Dengue is endemic to the Caribbean. Neurological complications that occur in severe dengue are extremely rare. Severe central nervous system involvement is a dangerous complication of dengue associated with a high mortality. No definite medical versus surgical management consensus exists as studies have highlighted varying outcomes for severe dengue with intracranial hemorrhage (ICH). Our case highlights a patient presenting with severe dengue complicated by an ICH and subsequent diabetes insipidus postoperatively further emphasizing this controversy.

KEYWORDS: case report, dengue, dengue with warning signs, severe dengue, dengue shock syndrome, subdural hematoma, intracranial hemorrhage, diabetes insipidus, neurological complication

INTRODUCTION

Dengue is a disease encompassing multiple presentations, an unpredictable course and outcome.¹ It may also progress to dengue with warning signs and life-threatening severe dengue and if not promptly treated may result in multi-organ dysfunction and subsequent death.¹ Neurological complications are extremely rare (<1%) in severe dengue with only a handful of cases of cerebral hemorrhage comprising acute subdural hematomas (SDH) being described.^(2,3) Jayasinghe et. al published the sole case of severe dengue with associated development of diabetes insipidus.⁴ No reported cases of severe dengue complicated by diabetes insipidus exist to date, highlighting the rarity of this occurrence.

Our case describes a middle-aged male presenting with a secondary dengue infection and the sequence of events as it progresses to severe dengue, his hospital course including development of a cerebral hemorrhage requiring neurosurgical intervention, intensive care unit (ICU) admission and diabetes insipidus.

CASE PRESENTATION

Day 1

The patient, a 65-year-old male, presented to his general practitioner complaining of a one-day history of passing black and dark red stool. He also reported a six-day history of fever, four-day history of decreased appetite, two-day history of nausea, one day history of abdominal pain and reported no bleeding, body aches, headaches, vomiting, skin rash and retroorbital pain. His past medical history was significant for a five-year history of type II diabetes mellitus and hypertension for which he was controlled on Metformin 1g and Enalapril 10mg respectively. He reported exposure to mosquitoes, no history of anticoagulant use and was subsequently referred to the emergency department of a tertiary care hospital.

On examination, his vital signs were BP 122/86 mmHg, HR 89 bpm, temperature 36.4°C, random blood glucose (RBS) 130mg/dl. Cardiovascular and respiratory examinations were unremarkable. His abdominal exam revealed a soft abdomen with mild tenderness in the epigastric region and an unremarkable digital rectal exam (DRE). His pupils were equal and reactive to light bilaterally with a Glasgow Coma Scale (GCS) of 15/15. Laboratory tests are presented in Table 1.

The patient was thrombocytopenic with a platelet count

of $9 \times 10^3/\mu\text{L}$ together with elevated liver enzymes. Pronounced hilar markings bilaterally were noted on his chest radiograph with no evidence of a pleural effusion. On admission to the medical ward, his working diagnosis encompassed:

- I. Acute viral illness with thrombocytopenia likely dengue fever
- II. Acute kidney injury secondary to dehydration
- III. Transaminitis
- IV. Diabetes Mellitus and Hypertension

Day 2 – Ward

While on the ward, the patient's GCS declined to 9/15 (E1 M6 V2). The onset of a left-sided hemiparesis and unequal pupils (right pupil 4mm, unreactive and left pupil 2mm, sluggish) led to a referral to the Intensive Care Unit (ICU). Dengue IgG, IgM and NS1 antigen titers returned positive. A CT Brain was requested but while waiting for the scan a further decline in GCS to 7/15 (E1 M5 V1) occurred. In addition, continued deterioration in HCT, total protein, Hb and platelet counts were noted, evidenced in Table 1. No platelet clumping was visualized on manual blood film.

A non-contrast CT brain revealed a large right-sided acute subdural hematoma (SDH) with 1.6 cm midline shift to the left and mass effect (Figure 1).

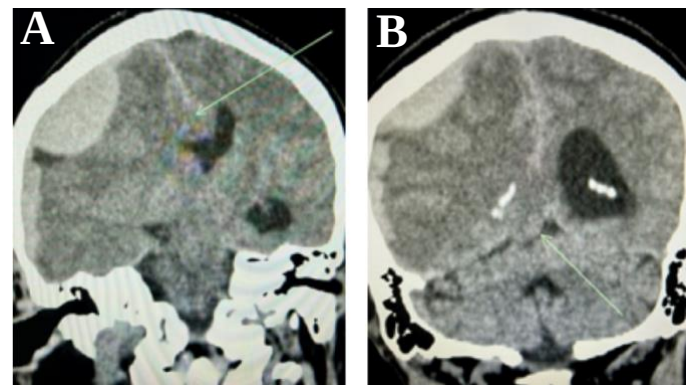


Figure 1: Non-contrast CT Brain showing a large acute right subdural hematoma with (A) subfalcine and (B) transtentorial herniation

A decision for emergent right craniotomy and SDH evacuation was taken after neurosurgical review and further decline of GCS to 5/15 (E1 M3 V1). Estimated blood loss intra-operatively was 2.5 liters. Perioperatively, Tranexamic Acid 1g IV as well as one unit of PRBC, six units of fresh frozen plasma (FFP) and six units of platelets were administered. Vasopressor support was initiated intraoperatively and the patient was subsequently transferred to ICU for multi-organ support as he progressed to severe dengue.

Table 1: Trend of Laboratory Values with Reference Ranges

	Admission	Day 2 Ward	Day 3 ICU	Day 4 ICU	Reference Range
White Blood Cell	6.8	7.7	8.39	5.68	3.1-8.50 x 10 ³ /uL
Hemoglobin	17.7	13.2	7.9	8.3	12.4-14.9 g/dL
Platelet	9	7	57	102	156-373 x 10 ³ /uL
Hematocrit	49	37	22.1	26.5	36-43.6%
Sodium	136	137	138	154	135-145 mmol/L
Potassium	4.9	5.1	4.8	4.4	3.5-5.1 mmol/L
Blood Urea Nitrogen	40	35	25	20	6-23 mg/dL
Creatinine	2.3	1.4	1.1	2.6	0.7-1.2 mg/dL
Aspartate Aminotransferase	119.3	86.3	48.9	37.6	5-40 IU/L
Alanine Aminotransferase	69.5	47.2	33.3	20.1	5-41 IU/L
Alkaline Phosphate	NR*	NR*	54	97	35-104 U/L
Gamma Glutamyl-transpeptidase	180	134	60	58	5-36 U/L
Total Protein	5.9	NR*	5.0	4.1	6.4-8.3g/dL
Prothrombin Time	10.6	NR*	12.3	11.5	9.5-13.5 seconds
Partial Thromboplastin Time	41.8	NR*	38.8	34.5	27-35 seconds
International Normalized Ratio	1.0	NR*	1.18	1.09	0.8-1.2
Dengue IgG	Positive	Positive			
Dengue IgM	Negative	Positive			
Dengue NS1 Antigen	Negative	Positive			

*NR – no result

Day 3 – ICU Admission

ICU management commenced with neuroprotection and successful weaning of vasopressor support. The patient's sedated GCS of 2T/15 with pupils 3mm bilaterally, non-reactive to light were apparent. Furthermore, a reduction in creatinine to 1.1mg/dL was noted along with improvement of the metabolic acidosis.

The patient experienced a recurrence of the upper gastrointestinal bleeding (UGIB), evidenced by nasogastric coffee ground drainage. His laboratory values showed a fall in Hb to 7.9g/dL, HCT 22.1%, platelet 57 x 10³/uL, prothrombin time (PTT) 38.8 seconds and BUN 25mg/dL (Table 1). His treatment regime consisted of a PRBC transfusion and a Proton Pump Inhibitor (PPI) infusion with no further investigation.

Day 4 - ICU

The patient became polyuric, with an increase in serum sodium from 138mmol/L to 153 mmol/L, a decreased urine osmolality 150mOsm/kg and an increased plasma osmolality 326mOsm/kg indicating diabetes insipidus. His sedation was discontinued for neurological assessment and a repeat CT Brain requested. Vasopressor requirements increased significantly, urine output decreased and creatinine increased to 2.6mg/dL. His sodium continued to rise to 154mmol/L (Table 1) and there was no improvement in neurological status despite sedation cessation. Additionally, spontaneous breathing was no longer noted and his cough and gag reflex was absent.

Repeat CT Brain uncovered a smaller SDH with extracranial extension, an acute intraparenchymal

hemorrhage with intraventricular extension, reduced midline shift, and severe extracranial and cerebellar tonsillar herniation (Figure 2).



Figure 2: Non-contrast CT Brain post-craniotomy and evacuation of subdural hematoma showing an acute intraparenchymal hemorrhage with intraventricular extension and reduced midline shift

His CT findings rendered water deprivation tests and desmopressin to distinguish between central or nephrogenic DI useless. Brainstem testing was conducted by two consultant physicians eight hours apart confirming brainstem death.

DISCUSSION

Dengue is caused by a RNA virus that is transmitted by the bite of an infected *Aedes Aegypti* mosquito.⁵ In June 2024, Pan American Health Organization (PAHO) reported more than 9,500 cases of severe dengue associated with over 4,500 deaths in the Caribbean region.⁶ The onset of the rainy season brought with it an increase in the breeding grounds for this vector leading to the development of an epidemic in this country.⁵

The World Health Organization (WHO) requires abdominal pain or tenderness, persistent vomiting, fluid accumulation, mucosal bleed, lethargy, restlessness, liver

enlargement and increasing hematocrit with decreasing platelets to confirm the diagnosis of dengue fever with warning signs.¹ Severe dengue is defined as dengue with severe plasma leakage, severe hemorrhage or severe organ impairment.¹ Our patient fulfilled these conditions eventually requiring vasopressor infusions to maintain his MAP and cerebral perfusion pressure (CPP).

The NS1 antigen is a viral protein released early in the course of the disease and can be used before day five of illness to detect infection.⁷ IgG and IgM antibodies are a cheaper alternative but are only detectable after five days of fever and can be a limiting factor for diagnosis.⁷ NS1 antigen and both IgG and IgM antibodies were positive in our patient, indicating a secondary infection. Nucleic Acid Amplification Test (NAAT) is the gold standard investigation for dengue however these facilities were unavailable in our low-resource setting.

Kulkarni et. al showed the common neurological sequelae of severe dengue ranged from encephalopathy and syncope to encephalitis, with intracranial hemorrhage (ICH) being rare.⁸ They attributed the ICH associated with severe dengue to severe thrombocytopenia and a deranged coagulation profile, similar to our patient. Guidelines indicating the timing of CT are not available therefore a high index of clinical suspicion, on a background of dengue with warning signs, prompted imaging due to a drop in our patient's GCS.

Management of ICH in severe dengue remains controversial. Factors such as neurosurgical facilities, surgeon experience, availability of blood and blood products and patient comorbidities all contribute to the clinical outcome hence the dilemma of surgical versus conservative medical management persists.⁹ Sam et al. described poor outcomes after neurosurgical intervention in nine patients of varying ages, comorbidities and thrombocytopenia with secondary dengue infection and severe ICH.² In contrast, Ashraf et al. detailed a case of a 65-year old patient with a secondary dengue infection and thrombocytopenia presenting with ICH and decreased GCS who underwent successful neurosurgical intervention.³ These reports highlight the variability in outcome of surgical management in this rare condition.

The decision to transfuse a patient with dengue fever with warning signs requires consideration of multiple factors. The WHO does not recommend transfusion of FFP and platelets in the patient with severe bleeding defined as persistent bleeding, decreased hematocrit, refractory shock, worsening metabolic acidosis and hemodynamic instability.¹ However, Lye et al. highlighted the

importance of platelet transfusion as both prophylactic and therapeutic management, with a transfusion trigger of $<10 \times 10^3/\mu\text{L}$ in the absence of hemorrhage.¹⁰ His multicenter, open-label, superiority trial explored prophylactic platelet transfusions versus supportive care in dengue with platelet count $<20 \times 10^3/\mu\text{L}$. Of the 369 patients enrolled in the trial, 187 patients were randomly assigned to the transfusion group and 182 patients to the control group. Patients in the transfusion group received four units of platelets every day if their platelet count was $<20 \times 10^3/\mu\text{L}$ whilst those in the control group received anti-pyretics, analgesia, bed rest and fluid therapy. The primary outcome was clinical bleeding, exclusive of petechiae, until hospital discharge or within seven days of randomization and it occurred in 21% of patients in the transfusion group and 26% of patients in the control group ($p=0.16$). The study reported 13 adverse events in the transfusion group with 2 incidents in the control group ($p=0.0064$) leading to the conclusion that transfusions were not better than supportive care, but that it may be correlated with adverse events of anaphylaxis, transfusion related acute lung injury (TRALI) and fluid overload.¹⁰ Our patient had an initial platelet count of $9 \times 10^3/\mu\text{L}$ but no platelet transfusions were initiated due to the absence of further episodes of bleeding. Nonetheless, he received platelet and FFP transfusions in the perioperative period after the diagnosis of his ICH.

Thromboelastography (TEG) is being advocated to assess the clotting abnormalities in dengue with warning signs and guide product transfusion to reduce the associated adverse effects. Vijayan et al. highlighted deficiencies in coagulation factors being responsible for the primary source of bleeding rather than platelet dysfunction.¹¹ Hence, FFP may be more prudent as a source of factor replacement to quell the bleeding manifestations in dengue with warning signs. However, early recognition and treatment of these deranged hematologic profiles is paramount to reduce hemorrhagic manifestations and progression to severe dengue.

Diabetes Insipidus is characterized by the loss of water homeostasis caused by the lack of antidiuretic hormone release from the pituitary gland.⁴ Our patient developed hypernatremia (sodium $>145\text{mmol/L}$), hypotonic polyuria ($>50\text{ml/kg/24h}$), increased plasma osmolality ($>300\text{mOsm/kg}$) and a decreased urine osmolality ($<200\text{mOsm/kg}$) fulfilling the diagnostic criteria for central diabetes insipidus.⁴ A nephrogenic cause of the diabetes insipidus was ruled out due to resolution of his acute kidney injury. A confirmatory water deprivation test was not conducted as repeat imaging demonstrated

catastrophic intracranial pathology, leading to clinical deterioration and the diagnosis of brainstem death. Interestingly, the occurrence of diabetes insipidus associated with ICH in dengue with warning signs is rare but the two cases that have been reported culminated in the death of the patients, one of whom received neurosurgical intervention⁴ demonstrating the variable outcomes in dengue despite adequate supportive management.

CONCLUSION

Our patient developed an ICH, underwent evacuation but subsequently developed diabetes insipidus due to cerebral edema and new ICH with significant extension leading to herniation and eventual death. It is important to be aware of these hemorrhagic manifestations in patients presenting with dengue with warning signs. Any changes in GCS should prompt imaging, careful management of hematologic parameters and a decision for surgery based on the patient's clinical status, comorbidities and physiological reserve, due to the unpredictable nature of its outcome.

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