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Dengue fever with bilateral thalamic diffusion restriction lesions: a case report

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Abstract

Background Dengue encephalitis is a rare complication of dengue and can manifest as ischemic stroke, making the diagnosis challenging. This case highlights the need of recognizing unusual presentation of dengue and the use of neuroradiology in its diagnosis.

Case presentation A previously healthy 38-years-old man presented to the emergency department with weakness of the left upper limb and bilateral lower limbs, aphasia and confusion. He had flu-like symptoms along with fever for the past 3 days. Magnetic Resonance Imaging (MRI) of the brain showed hyperintensities in the bilateral thalamic and parafalcine regions. The patient was started on aspirin for the suspicion of ischemic stroke. But the patient's condition deteriorated. Lumbar puncture did not reveal any evidence of meningitis. The blood Reverse Transcription Polymerase Chain Reaction (RT-PCR) confirmed the diagnosis of dengue hemorrhagic fever.

Conclusions This article emphasizes the importance of including the complications and manifestations of dengue fever in the differential diagnosis of ischemic stroke in a relevant context. Unique radiological finding of bilateral thalamic lesions can serve as important diagnostic clues in such atypical cases. Early diagnosis can help guide therapy.

Keywords Dengue encephalitis, Bilateral thalamic lesions, Ischemic stroke

Background

Dengue fever, an arboviral illness, is a global health problem affecting 129 countries and 5.2 million people per year [1]. It is spreading rapidly in new geographical entities in addition to the previously affected areas [2]. Although fever, myalgia, and thrombocytopenia are the common clinical features, neurological symptoms occur rarely in 0.5–20% of the cases [3]. We describe a case of dengue fever with neurological symptoms and MRI findings resembling ischemic stroke, that highlights the diagnostic challenges in dengue encephalitis.

Case presentation

A previously healthy 38-years-old male presented to the Emergency Department with weakness of left upper limb and bilateral lower limbs. He had a fever with flu-like symptoms for the past three days. He had no history of headache, vomiting, trauma or seizures. On physical examination, he had grade 3/5 motor strength (Medical Research Council (MRC) scale) in the left upper and lower limbs and grade 4/5 motor strength in the right lower limb. On mental status examination the patient was alert but disoriented and aphasic. His Glasgow Coma Scale (GCS) score was 11. Pupils were equal, round, and reactive to light. No asymmetry was noted on facial

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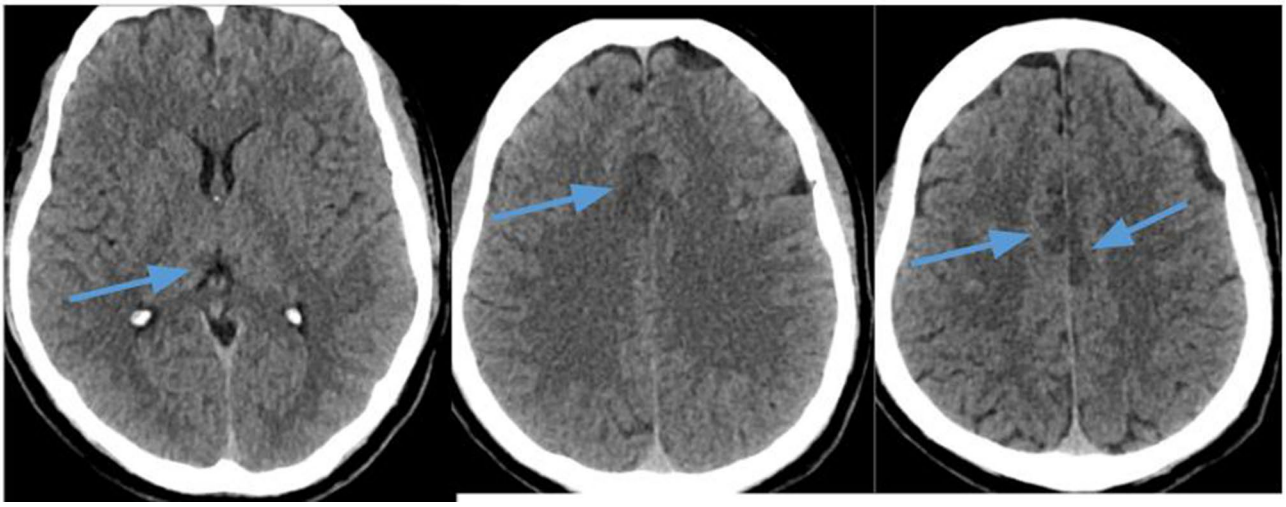

Fig. 1 Non-Contrast CT head showing bilateral thalamic and parafalcine low attenuation regions

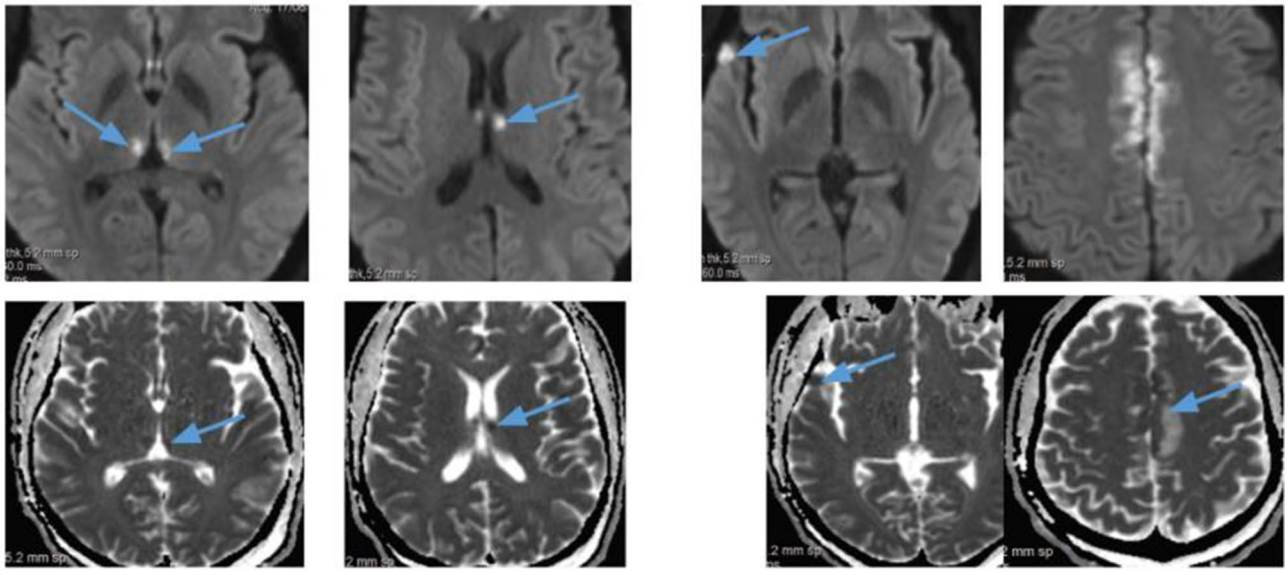

Fig. 2 Diffusion weighted imaging (DWI) and Apparent Diffusion Cofficient (ADC map) showing areas of diffusion restriction within these lesions as evidenced by high signal on DWI and low signal on ADC map

examination. Extraocular movements were normal, and there was no nystagmus or ptosis. There were no rashes or fever. His initial vitals were: temperature 36.6 °C, pulse rate 84 bpm, blood pressure 122/74 mmHg, respiratory rate 18 breaths per minute and oxygen saturation 97%.

Complete blood count revealed hemoglobin 160 g/L (normal:132–173 g/L), hematocrit 0.465 (normal:0.390–0.490), white blood cell count 4.15 × 10^9/L (normal:4–11 × 10^9/L) (lymphocytes 0.54 × 10^9/L (normal:1-3.5 × 10^9/L), neutrophils 3.42 × 10^9/L (normal: 2–8 × 10^9/L)) and platelets 180 × 10^9/L (normal:140–400 × 10^9/L). Coagulation panel included activated Partial Thromboplastin Time (aPTT) 36.2 s (normal:28.6–38.2), International Normalized Ratio (INR) 1.04 (normal:0.82–1.2), Prothrombin Time (PT) 13.3 s (normal: 11.5–14.5). Serum chemistry revealed glucose 8.27 mmol/L (normal:2.8–8.8 mmol/L) and lactate 4.9 mmol/L (normal:0.5–2.2 mmol/L).

A Computerized Tomography (CT) scan of the brain showed low attenuation in the bilateral superior frontal parafalcine region (Fig. 1). The patient was diagnosed with suspected acute ischemic stroke in bilateral anterior cerebral artery (ACA) regions and was started on aspirin and atorvastatin. An MRI revealed bilateral thalamic and parafalcine areas of diffusion restriction with haemosiderin deposition raising suspicion of bilateral ACA territory infarcts and artery of Percheron infarct (Figs. 2, 3 and 4). Echocardiogram showed mild to moderate

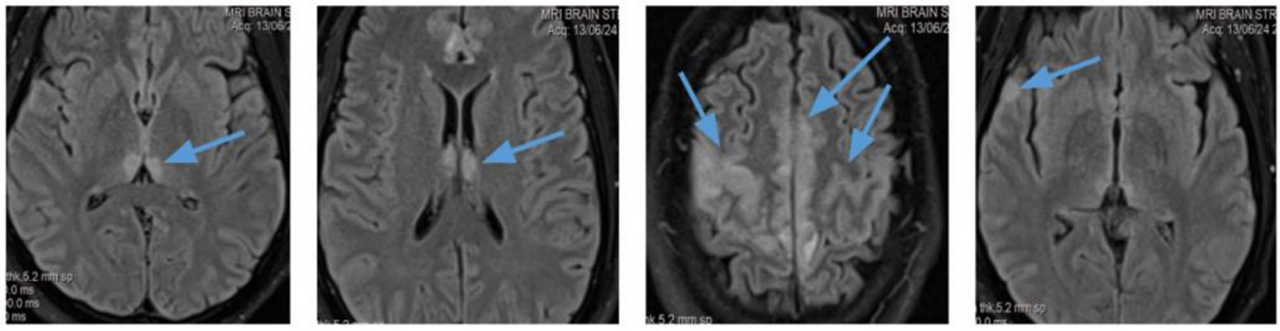

Fig. 3 Multifocal lesions in bilateral thalami, right temporal lobe, bilateral frontal lobes showing Fluid Attenuated Inversion Recovery Sequence (FLAIR) hyper intense signal change

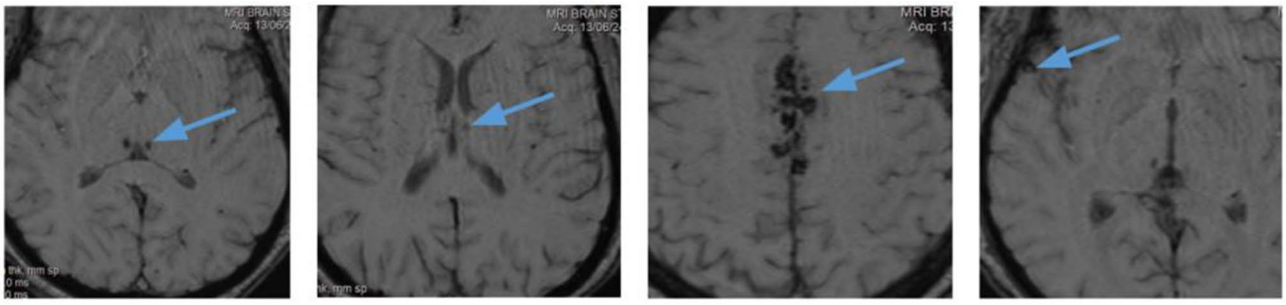

Fig. 4 Susceptibility Weighted Imaging (SWI) revealing bilateral thalamic and parafalcine artefact in keeping with hemosiderin deposition

decrease in left ventricular function with an ejection fraction of 40–45%.

The next day, the patient developed a large amount of dark stool. A CT scan of the abdomen showed no evidence of an active hemorrhage in the large and small bowels. Colonoscopy revealed extensive bleeding and widespread inflammation throughout the terminal ileum and colon.

Despite fluid resuscitation, the patient's condition deteriorated. He had tachycardia, fever, and was acidotic. His pH was 7.3 (normal: 7.35–7.45). And GCS score dropped to 9 and a purpuric rash appeared on the right hypochondriac and flank areas.

Complete blood count revealed hemoglobin 194 g/L (normal:132–173 g/L), hematocrit 0.557 (normal:0.390–0.490), white blood cell count 13.11 × 10^9/L (normal:4–11 × 10^9/L) (lymphocytes 0.82 × 10^9/L (normal:1-3.5 × 10^9/L), neutrophils 11.57 × 10^9/L) (normal: 2–8 × 10^9/L) and platelets 212 × 10^9/L (normal:140–400 × 10^9/L). Coagulation panel included aPTT 38.6 s (normal:28.6–38.2), INR 1.19 (normal:0.82–1.2), PT 15.1 s (normal: 11.5–14.5).

He was transferred to the intensive care unit (ICU) where he was intubated, and general surgery was consulted. Given the fever (39.2 °C) and altered mental status, a lumbar puncture (LP) was performed, and he was started on antibiotics. Cerebrospinal fluid (CSF) analysis revealed red blood cell count 330 × 10^6/L, white blood cell count 4 × 10^6/L (normal:0-5 × 10^6/L) (neutrophils 20% (normal:0–6%), lymphocytes 65% (normal:40–80%), monocytes 15% (normal:15–45%)), protein 0.92 g/L (normal:0.15–0.45 g/L), glucose 6.27 mmol/L (normal: 2.22–3.89 mmol/L), lactate 3.2 mmol/L (normal:1.1–2.4 mmol/L).

BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel (bioMérieux, Lyon, France). for common viral and bacterial pathogens was negative. Blood and CSF cultures were negative.

Coagulation tests revealed fibrinogen 3.17 g/L (normal:1.9–4.3 g/L), DRVV Screen 0.84 (normal: </= 1.2), negative PAT screen (29.1), negative REF screen (34.8), D-dimer 3.64 mcg/mL (</= 0.5 mcg/Ml) and PTT-LA 38.5 s (normal: 29–45). Immunology tests revealed negative cANCA (< 2RU/mL) and pANCA (< 2RU/mL), C-reactive protein 68.6 mg/L (normal: </=5 mg/L), cardiolipin IgG 2.7 CU (normal: </=20), cardiolipin IgM 2.5 CU (normal: </=20), and DNA Ab < 9.8 IU/mL (normal:</=26), ENA screen < 3.6 CU (normal: </=20) and negative syphilis TP screen.

On Day 3, Reverse Transcription Polymerase Chain Reaction (RT-PCR) for dengue turned positive. The IgM test result for dengue was 1.95 and serotyping was dengue virus 2 strain (DENV2). While the patient initially had a normal platelet count, it began to decrease on day 2, falling below normal on day 3, and then started to rise again on day 8.

Detailed results came out for CSF encephalopathy autoimmune/paraneoplastic evaluation (Mayo Clinic Laboratories, Rochester, Minnesota, USA), and tests were negative for the following antibodies: AMPA-R Ab CBA (AMPCC), Amphiphysin Ab (AMPHC), Anti-Glial Nuclear Ab, Type 1 (AGN1C), Anti-Neuronal Nuclear Ab, Type 1 (ANN1C), Anti-Neuronal Nuclear Ab, Type 2 (ANN2C), Anti-Neuronal Nuclear Ab, Type 3 (ANN3C), CASPR2-IgG CBA (CS2CC), CRMP-5-IgG (CRMC), DPPX Ab CBA (DPPCC), GABA-B-R Ab CBA (GABCC), GAD65 Ab Assay (GD65C), GFAP IFA (GFAIC), mGluR1 Ab IFA (GL1IC), IgLON5 CBA (IG5CC), LGI1-IgG CBA (LG1CC), Neurochondrin IFA (NCDIC), NIF IFA (NIFIC), NMDA-R Ab CBA (NMDCC), Purkinje Cell Cytoplasmic Ab Type Tr (PCTRC), Type 1 (PCA1C), Type 2 (PCA2C), PDE10A Ab IFA (PDEIC), Septin-7 IFA (SP7IC), and TRIM46 Ab IFA (T46IC).

Serum encephalopathy autoimmune/paraneoplastic evaluation (Mayo Clinic Laboratories, Rochester, Minnesota, USA) was also conducted, and tests were negative for the following antibodies: Alpha Internexin CBA (AINCS), AMPA-R Ab IF Titer Assay (AMPIS), Amphiphysin Immunoblot (AMIBS), ANNA-1 Immunoblot (AN1BS), ANNA-2 Immunoblot (AN2BS), CRMP-5-IgG Western Blot (CRMWS), DPPX Ab IFA Titer (DPPTS), GABA-B-R Ab IF Titer Assay (GABIS), GFAP CBA (GFACS), GFAP IFA Titer (GFATS), IgLON5 IFA Titer (IG5TS), mGluR1 Ab CBA (GL1CS), mGluR1 Ab IFA Titer (GL1TS), NIF Heavy Chain CBA (NFHCS), NIF IFA Titer (NIFTS), NIF Light Chain CBA (NFLCS), NMDA-R Ab IF Titer Assay (NMDIS), PCA-1 Immunoblot (PC1BS), PCA-Tr Immunoblot (PCTBS), AGNA-1 Titer (AGNTS), Amphiphysin Ab Titer (APHTS), ANNA-1 Titer (AN1TS), ANNA-2 Titer (AN2TS), ANNA-3 Titer (AN3TS), CRMP-5-IgG Titer (CRMTS), Neurochondrin CBA (NCDCS), Neurochondrin IFA Titer (NCDTS), PCA-1 Titer (PC1TS), PCA-2 Titer (PC2TS), PCA-Tr Titer (PCTTS), Septin-7 CBA (SP7CS), Septin-7 IFA Titer (SP7TS), PDE10A Ab IFA Titer (PDETS), TRIM46 Ab CBA (T46CS), and TRIM46 Ab IFA Titer (T46TS).

Serum copper was 116 mcg/dL (normal: 73–129 mcg/dL) and serum zinc was 31 mcg/dL (normal: 60–106 mcg/dL).

Treatment included supportive therapy, fluids, and deep venous thrombosis prevention. Intracranial angiography and venography was unremarkable.

During his ICU stay, the patient's condition gradually improved and he was transferred to the ward.

A repeat MRI was performed on the 5th day of admission. The lesions show interval evolution on Fluid Attenuated Inversion Recovery sequence (FLAIR) and Susceptibility Weighted Imaging (SWI) imaging (Fig. 5).

An electroencephalography (EEG) was performed on the sixth day of admission in standard 10–20 electrode placement system with banana montage. It did not reveal any epileptiform discharges or active seizures. However, it did show slowing of the background rhythm continuous in theta range 5–6 Hz, which was consistent with an encephalopathic pattern (Fig. 6).

He regained upper body strength, and he became more responsive and communicative. However, residual lower limb weakness persisted (1–2/5 on MRC scale). At the time of discharge (day 24 of hospital stay) to rehabilitation his Modified Rankin Scale (MRS) score was 4.

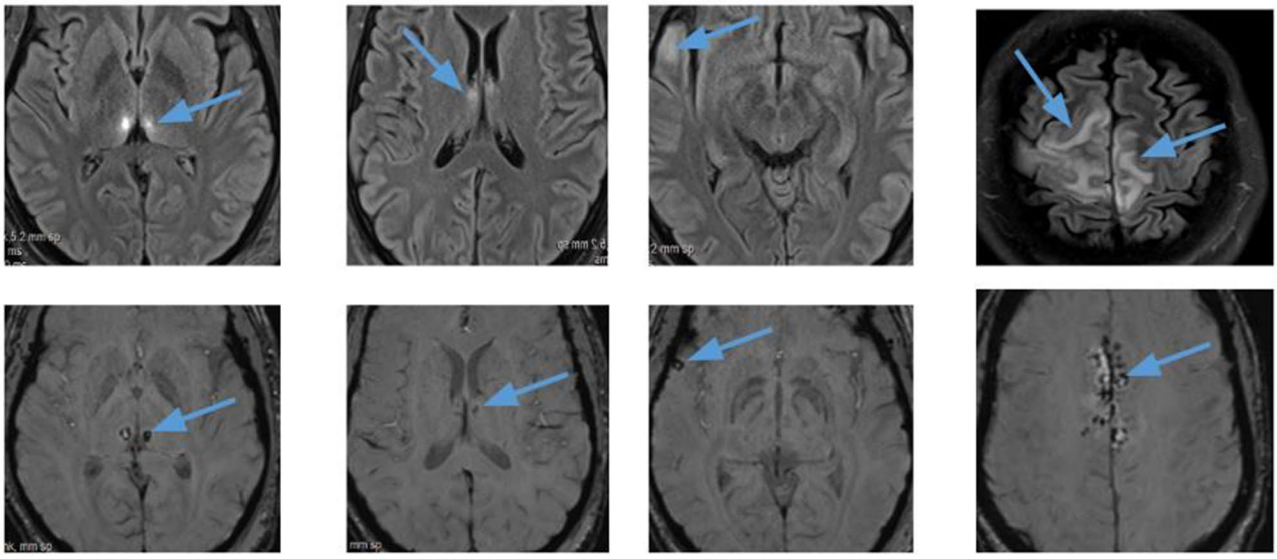

Fig. 5 Interval evolution on FLAIR and SWI imaging

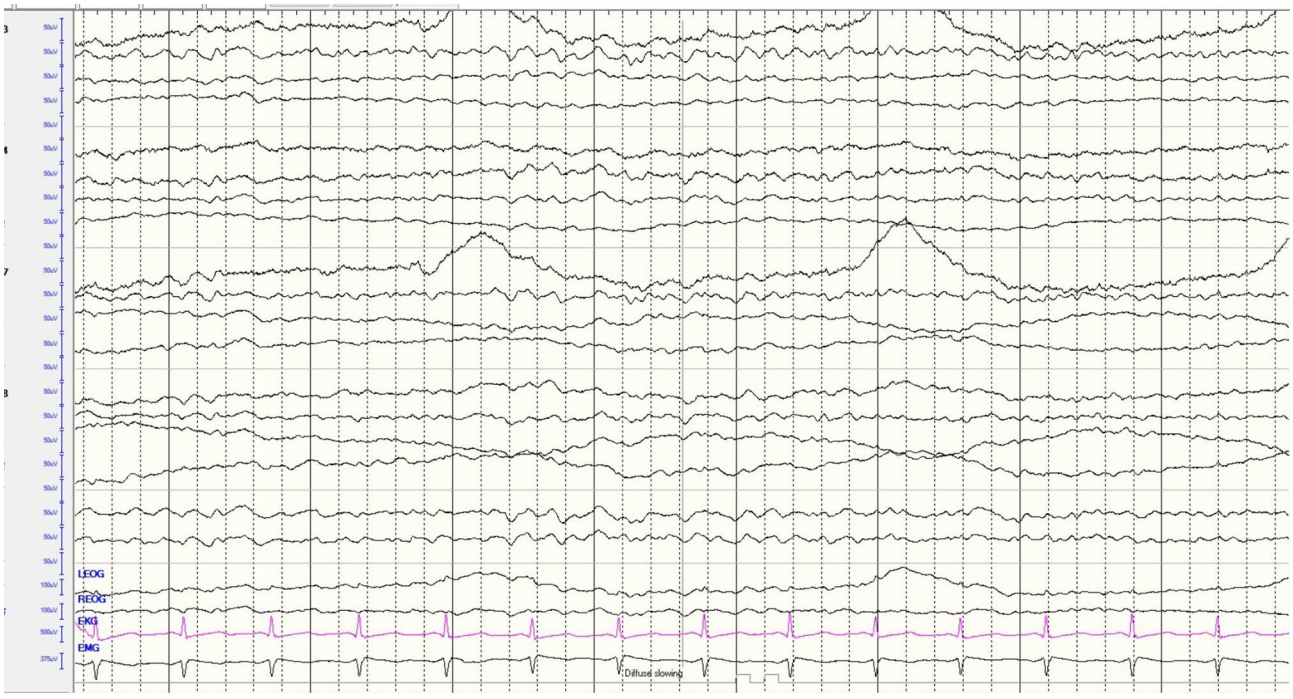

Fig. 6 EEG showing slowing of background rhythm

Discussion and conclusions

We report a case with two uncommon features of dengue fever including bilateral thalamic restriction lesions and being diagnosed in a geographical location where it has been previously extremely rarely reported.

Dengue fever can present from asymptomatic to severe multi-organ failure with common findings being fever, myalgia, retro-orbital pain and thrombocytopenia. Neurological involvement occurs in 0.5–20% of cases and includes encephalitis, meningitis, strokes (both hemorrhagic and ischemic), myositis, rhabdomyolysis, myelitis, encephalopathy and Guillain-Barré syndrome [3–5]. The occurrence of dengue encephalitis is even rarer and is estimated to be between 0.5% and 6.2% [6, 7]. The neuropathogenesis of dengue is thought to involve direct invasion, autoimmune reactions, and metabolic disturbances.

Our patient presented with bilateral thalamic diffusion-weighted imaging (DWI) lesions. Few such cases linked to dengue illness have been previously documented in the literature. The interpretation of these bilateral thalamic DWI lesions in patients with dengue fever has been inconsistent and variably reported as dengue-associated meningoencephalitis or as artery of Percheron stroke [8–11]. In our patient the initial diagnosis was considered to be possible artery of Percheron infarct. Later with the evolution of the clinical picture and availability of new data, the findings met Soares and Puccioni-Sohler's diagnostic criteria for dengue encephalitis. These include fever, altered consciousness, and positive dengue PCR [12].

Furthermore, the DWI and ADC imaging continued to demonstrate similar signal on the MRI 4 days later. In case of an ischemic lesion, we would expect the signal to normalize by this time which did not happen in this case. This can pose a challenging diagnostic dilemma.

In the documented cases of ischemic stroke-like lesions linked to dengue illness [8–11], it is not clear whether those lesions with restriction in diffusion are due to true ischemia as seen in vascular occlusion or due to edema as part of dengue encephalitis. Post-mortem examination of two patients with dengue encephalitis with the typical MRI features of bilateral thalamic DWI positive lesions showed areas of marked edema, congested dilated capillaries and hemorrhages [13]. This would argue against typical ischemic infarcts. Moreover, the lesions seen in dengue fever seem to be symmetric bilateral and not always respecting a vascular territory. In addition, there is microhemorrhage seen very frequently on the susceptibility imaging much more frequently than what is observed in classic vascular infarcts.

Although dengue is currently extremely rare in our region, the area is regarded as a potential breeding ground for Aedes aegypti mosquitoes [14–17]. This is possibly linked to alterations in temperature, humidity and precipitation caused by climate change. This pattern has been seen in a number of places in our neighbouring region where dengue outbreaks have been closely linked to excessive rainfall [18, 19]. This makes dengue an emerging infection in regions where it was previously uncommon. When a patient with dengue presents in

such regions, especially with an unusual clinical presentation, it tests the diagnostic skills and clinicians need to proactively look for it.

Our case report has several limitations. We do not have the CSF dengue PCR result. As dengue is epidemiologically not among the top differential diagnoses, it was initially not tested when the LP was performed. Later with the hemorrhagic manifestations, Crimean-Congo hemorrhagic fever was considered and Dengue was considered as a differential. Secondly, while it is difficult to completely exclude aspirin as a contributing factor, the patient's clinical deterioration—evidenced by worsening tachycardia, fever, acidosis, a drop in GCS from 11 to 9, and the appearance of a purpuric rash—aligns more closely with the natural progression and complications of dengue encephalitis. Furthermore, while hemorrhagic changes were observed on the brain MRI, the lack of significant hemorrhagic events in other areas, despite aspirin use, suggests that the primary cause of the patient's deterioration was related to the dengue pathology rather than the effects of aspirin. Thirdly, nonstructural protein 1 (NS1) wasn't done in this case. We acknowledge that NS1 could have further helped in confirming the diagnosis, but we believe the positive IgM, the serotyping and the low zinc level provides strong support for a recent dengue infection [20]. Cross-reactivity between dengue virus and tick-borne encephalitis virus (TBEV) is possible due to shared epitopes on flavivirus envelope proteins, leading to diagnostic uncertainty in serological tests [21]. However, TBEV is rare in the Middle East due to the limited presence of Ixodes tick vectors, making dengue the primary flavivirus concern in this region. In our case, RT-PCR confirmed dengue infection with high specificity, bypassing the limitations of serological cross-reactivity. While the absence of NS1 antigen testing and TBEV-specific assays are limitations, the clinical, imaging, and molecular findings strongly support dengue-associated encephalopathy as the diagnosis. Our patient wasn't tested for Japanese encephalitis. While Japanese encephalitis is a concern in certain regions, it is not commonly encountered in the Middle East, which is why it was not part of the initial investigation. However, we did conduct an RT-PCR test for Crimean-Congo hemorrhagic fever, and the result came back negative. The combination of normal platelet counts, bilateral cerebral lesions, and terminal ileo-colitis is rare in dengue fever. However, in this case, these manifestations are likely linked to dengue rather than being coincidental. While platelet levels fluctuate during the disease, the presence of neurological and gastrointestinal symptoms indicates dengue's potential to affect multiple organ systems.

In conclusion, this case highlights the need to think of dengue fever while considering the differential diagnosis of bilateral thalamic diffusion restriction areas in a relevant context. Furthermore, it raises the awareness of the emergence of dengue fever in new geographical areas possibly due to climate change and new patterns in rainfall. This case highlights the broader spectrum of systemic involvement in dengue, contributing to our understanding of its diverse clinical presentations.

Abbreviations

MRI	Magnetic Resonance Imaging
RT-PCR	Reverse Transcription Polymerase Chain Reaction
MRC	Medical Research Council
aPTT	activated Partial Thromboplastin Time
INR	International Normalized Ratio
PT	Prothrombin Time
CT	Computerized Tomography
ACA	Anterior Cerebral Artery
ICU	Intensive Care Unit
LP	Lumbar Puncture
CSF	Cerebrospinal Fluid
DENV2	Dengue Virus Serotype-2
FLAIR	Fluid Attenuated Inversion Recovery Sequence
SWI	Susceptibility Weighted Imaging
MRS	Modified Rankin Scale
EEG	Electroencephalography
DWI	Diffusion-Weighted Imaging
ADC	Apparent Diffusion Coefficient
NS1	Nonstructural protein 1

Author contributions

HY, SD and UF prepared the manuscript. SD supervised the preparation of the manuscript. JA contributed critical revisions of the manuscript. ZH interpreted the radiological imaging. SD and HY critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent to participate

Informed consent was obtained from the participant included in the study.

Consent to publish

The participant has consented to the submission of the case report to the journal. The authors affirm that human research participant provided informed consent for publication of the images in Figs. 1, 2, 3, 4, 5 and 6.

Competing interests

The authors declare no competing interests.

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