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Dengue encephalitis: what's new?

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Purpose of review
Neurological manifestations of dengue (NeuroDengue) are uncommon but can often mimic those of other tropical infections. This review aims to present new insights on dengue encephalitis, emphasizing pathogenesis, clinical features, and diagnostic challenges. We highlight unique neuroimaging patterns, observed through MRI, which may aid in diagnosing NeuroDengue. The aim is to significantly enhance early recognition and management of this underreported but severe complication of dengue, providing valuable insights for healthcare professionals.

Recent findings
Recent research has improved our understanding of dengue encephalitis and the neurotropism of the dengue virus in regions such as the thalamus, basal ganglia, and cortex. Notable MRI findings include the 'double doughnut' sign and microhaemorrhages, although these findings are nonspecific and may also appear in other flavivirus encephalitides. A definitive diagnosis requires a positive cerebrospinal fluid (CSF) PCR for the dengue virus, often combined with antibody testing in both CSF and serum. Additionally, elevated levels of IL-6 and TNF-α in CSF indicate enhanced inflammatory responses, which strengthens the early identification of dengue encephalitis and informs potential management strategies.

Summary
Evidence affirms the neurotropic nature of dengue, confirmed by positive CSF PCR results. MRI typically reveals T2 hyperintensities in specific brain areas, along with the presence of micro-haemorrhages, and the 'double doughnut' sign. Recent advancements in diagnostics include analysing CSF dengue antibody indices and neuroinflammatory markers. Dengue serotypes 2 and 3 exhibit heightened neurovirulence, with seizures occurring in 30–40% of cases. While supportive management with fluids is crucial, a subset of patients may benefit from intravenous, immunoglobulin (IVIG) and steroids. Early identification of dengue encephalitis could significantly improve patient outcomes.

Keywords
central nervous system, gengue virus, encephalitis

INTRODUCTION

Arthropod-borne encephalitis viruses represent a significant global public health challenge, with dengue virus (DENV) emerging as a particularly concerning pathogen [1]. Transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes, DENV causes an estimated 390 million infections annually [2]. As a member of the Orthoflavivirus genus, DENV comprises four distinct serotypes (DENV-1 through DENV-4) that induce only partial cross-protective immunity [3]. This immunological phenomenon leaves individuals in endemic regions vulnerable to sequential infections by different serotypes. While most infections result in mild febrile illness, severe cases can progress to life-threatening complications, including haemorrhage, shock, and multiorgan failure.

Among the neurological manifestations of DENV infection, encephalopathy and encephalitis are the most frequent complications [1,4–7]. These conditions affect patients across all age groups, from infants as young as 3 months to elderly individuals. The neurological spectrum of dengue is vast, encompassing encephalitis, myelitis, Guillain–Barré syndrome, and myositis [8–10]. While all serotypes demonstrate neurotropic potential, DENV-2 and DENV-3 are most strongly associated with severe neurological presentations [11]. DENV-4 has been identified in brain tissue and cerebrospinal fluid

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KEY POINTS

- The rising global incidence of dengue necessitates heightened awareness among healthcare professionals regarding potential neurological complications, particularly dengue encephalitis.
- Dengue serotypes 2 and 3 exhibit a stronger association with severe neurological manifestations, highlighting the importance of monitoring these specific strains in clinical settings.
- MRI findings such as T2 hyperintensities, thalamic lesions, and microhaemorrhages are critical for diagnosing NeuroDengue, but they require confirmation through qualitative/quantitative CSF PCR testing for definitive viral identification.
- Elevated levels of IL-6 and TNF-α in cerebrospinal fluid indicate significant neuroinflammation, which can aid in early diagnosis and inform treatment decisions.
- Although supportive care is essential, adjunctive treatments like intravenous immunoglobulin (IVIG) and corticosteroids may benefit certain patients, warranting further research into optimal management approaches for dengue encephalitis.

(CSF) of encephalitis patients, confirming its capacity for neuroinvasion [9,11,12].

This review synthesizes current knowledge on dengue encephalitis, focusing on the clinical manifestations, pathogenic mechanisms, diagnostic approaches, management, and patient outcomes.

EPIDEMIOLOGY

The global burden of dengue has exponentially increased in recent decades. The WHO has documented approximately 5.2 million cases, with endemicity across more than 100 countries [13]. Dengue is now endemic throughout tropical and subtropical regions, specifically in Southeast Asia, and on the rise in Africa, Eastern Mediterranean, and Western Pacific [10]. Asia bears the most significant disease burden, accounting for nearly 70% of cases worldwide. The year 2023 saw particularly high transmission, with 4.5 million cases in the Americas with 2300 fatalities, while Asian nations, including Bangladesh (321 000 cases), Malaysia (111 400), Thailand (150 000), and Vietnam (369 000), experienced significant outbreaks [6].

Several interconnected factors drive this epidemiological expansion. The primary vectors, *A. aegypti* and *A. albopictus*, have expanded their geographic range into previously unaffected regions [14]. Climate change and extreme weather events, including the 2023 El Niño phenomenon, have created favourable conditions for mosquito proliferation through elevated temperatures and increased rainfall [15]. Concurrently, healthcare systems weakened by the COVID-19 pandemic struggle to mount effective responses, while political instability, economic crises, and population displacements further hinder containment efforts [16].

RISK FACTORS AND DISEASE SPECTRUM

Severe dengue manifestations, including Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS), are influenced by multiple risk factors [1,2,17]. Secondary infection with a DENV serotype different from that seen in primary infection poses the most significant risk due to antibody-dependent enhancement (ADE) due to the original antigenic sin [1,3,18]. Additional risk factors include extremes of age, with children and elderly being most vulnerable. Comorbid conditions such as diabetes, obesity, and hypertension are also risk factors [19]. There seems to be a strong genetic predisposition, which links specific variants to severe dengue, based largely on genome-wide association studies [20,21]. A high viral load and an exaggerated host immune response contribute to disease severity, indicating the significance of early diagnosis and supportive management [22].

NEUROLOGICAL MANIFESTATIONS

The clinical presentation of dengue ranges from asymptomatic infection to severe dengue characterized by a haemorrhagic fever or shock syndrome [1–3]. Neurological complications occur in up to 25% of dengue cases, with DENV-2 and DENV-3 most frequently implicated [4,10,22–24]. Multiple epidemiological studies indicate that the central nervous system (CNS) is involved in 4–13% of dengue cases, with notable geographic variation: 20% in Thailand, 5–6% in Vietnam, and 15% in India [1]. Strikingly, in Rio de Janeiro, Brazil, DENV was identified as the causative agent in 47% of viral encephalitis cases and 10% of viral meningitis cases, emphasizing its growing neurotropic significance [25].

Neurological manifestations can be due to three distinct mechanisms: direct viral invasion into the CNS (encephalitis, meningitis, myelitis, and myositis); systemic complications (encephalopathy and stroke); and postinfectious syndromes (Guillain–Barré syndrome, optic neuritis, and acute demyelinating encephalomyelitis) [4,5,11,12,26].

CLINICAL DISTINCTIONS AND FEATURES

Dengue encephalopathy, characterized by altered consciousness secondary to metabolic derangements or shock, typically presents with normal CSF findings

[24]. In contrast, dengue encephalitis reflects direct CNS invasion, evidenced by CSF pleocytosis (>5 cells/μl), focal neurological signs, seizures, neuroimaging abnormalities, and either DENV-specific IgM, NS1 antigen, or PCR positivity in CSF [9].

Pathophysiological mechanisms of CNS involvement in dengue include direct viral neuro- invasion, cerebral hypoperfusion, hepatic encephalopathy, cerebral oedema, electrolyte imbalances, and intracranial haemorrhage [4–6,10,11,27]. Elevated levels of cytokines (IL-6, IL-10) and biomarkers (sVCAM-1) in the CSF of dengue encephalitis patients suggest exaggerated neuroinflammation and blood-brain barrier disruption [22,28,29].

Clinical reviews indicate that 55% of patients with neurological manifestations meet the criteria for severe dengue, with haematological (89%) and hepatic (47%) involvement being the most common [1,4]. Among neurologic clinical manifestations, encephalopathy predominates (31%), followed by encephalitis (15%) [10]. Other reported presentations include intracranial haemorrhage, posterior reversible encephalopathy syndrome (PRES), Guillain–Barré syndrome, and various neuromuscular disorders.

The classic triad of dengue encephalitis includes fever, headache, and altered mental status, often accompanied by seizures [4,10,23,25]. Focal neurological deficits, status epilepticus, and meningeal signs may also occur. Interestingly, about 50% of encephalitis cases lack typical dengue syndrome (myalgia, rash, and bleeding), indicating the importance of considering dengue in any acute encephalitis syndrome occurring in endemic regions [10].

PATHOGENESIS

The neuropathogenesis of dengue involves both direct viral invasion and immune-mediated mechanisms. Key viral proteins, particularly NS1 and NS3, facilitate CNS entry through blood–brain barrier disruption. NS1 promotes barrier breakdown via TLR4-mediated inflammation and degradation of tight junction proteins (claudin-1 and occludin), whereas NS3 protease activity compromises endothelial integrity [22,30–32]. The virus also employs immune cells (macrophages, monocytes) as 'Trojan horses' for CNS entry, with ADE amplifying this process through Fcγ receptor-mediated uptake [29,32,33].

Postmortem studies have confirmed DENV RNA and antigens in brain tissue, while animal models demonstrate that NS1 induces BBB leakage and neuroinflammation [31,32,34]. The resulting cytokine storm (IL-6, TNF-α, and CXCL10) drives immune cell recruitment and neuronal injury [28,35,36]. Genetic factors further modulate susceptibility, with HLA class I/II alleles and cytokine gene polymorphisms (TNF-α and IL-10) influencing disease severity [20,37]. Ongoing research explores additional genetic determinants in endothelial stability (CD209 and CLEC5A) and antiviral responses (IFN-γ and OAS1).

LABORATORY DIAGNOSIS OF DENGUE ENCEPHALITIS

Dengue is diagnosed through direct detection of the virus or by serological methods. In the first 2–3 days of illness, PCR is highly sensitive and specific for detecting the virus [3,38]. The NS1 antigen is also positive in early infection, with a sensitivity of over 90% in primary dengue cases during the first 5–7 days, though this drops to 60–80% in secondary infections [39]. The NS1 antigen test can also be performed on CSF samples, though it is less sensitive as compared to blood testing [40].

IgM antibodies become detectable in blood from day 4 onwards providing serological evidence of dengue infection [3]. A fourfold increase in IgG antibody titres from acute to convalescent serum samples confirms recent dengue infection. Detecting IgM antibodies in the CSF is particularly important as it suggests local antibody production within the nervous system. Comparing antibody levels between CSF and serum is informative; a CSF to serum IgM ratio greater than 1.5 strongly indicates CNS involvement [26,41,42]. Serum testing should always be done in parallel to help distinguish between acute and past infections. However, serological tests have limitations, including potential false positives after vaccination and cross-reactivity with other flaviviruses, such as Zika or yellow fever.

CSF analysis typically reveals mild to moderate increases in white blood cells (usually lymphocytes) and mildly elevated protein levels, generally between 50 and 100 mg/dl [3,10,42]. Unlike bacterial meningitis, glucose levels are typically normal or only slightly decreased. While nonspecific, these findings can support the diagnosis when combined with other test results.

Additional tests, like the hemagglutination inhibition test (HIT) and plaque reduction neutralization test (PRNT), are available but are rarely used in clinical practice due to their long turnaround times. Metagenomic sequencing can help identify the virus in complex cases, while analysis of inflammatory markers in CSF (such as IL-6 and TNF-α) may provide additional evidence of neuroinflammation [35,43–46]. A definitive diagnosis typically requires correlating multiple findings: positive PCR or serology in CSF, characteristic CSF changes, and compatible clinical presentation. Early and accurate diagnosis is crucial as neurological complications of dengue can be serious, and prompt recognition allows for

better management. In endemic regions, clinicians should maintain a high index of suspicion for CNS involvement in dengue patients presenting with neurological symptoms [10].

NEUROIMAGING

Dengue encephalitis predominantly affects deep grey matter structures, including the basal ganglia, thalamus, cerebellum, and cortical grey and white matter (Fig. 1a–f). On MRI, these lesions appear as T2/FLAIR hyperintensities, sometimes with restricted diffusion, indicating cytotoxic oedema [7,47–49] and susceptibility-weighted imaging (SWI) often reveals microhaemorrhages.

In severe cases, such as dengue-associated acute necrotizing encephalitis (Dengue ANEC), bilateral thalamic haemorrhages may occur, resembling findings in other flavivirus infections. Bilateral thalamic T2 hyperintensities with a concentric layered appearance, due to haemorrhage and surrounding oedema is a distinctive radiological feature on MRI described as the 'double doughnut' sign (Fig. 1d) [50,51]. The MRI apparent diffusion co-efficient (ADC) axial section usually shows central haemorrhagic necrosis, with a hypointense rim of cytotoxic oedema showing diffuse restriction, surrounded by a hyperintense rim of vasogenic oedema [52]. However, this finding is not pathognomonic for dengue, as similar patterns occur in Japanese encephalitis, West Nile virus, rabies, and herpes simplex encephalitis [53].

THERAPEUTIC APPROACHES

Current management of dengue encephalitis remains primarily supportive as no specific antiviral therapy has yet been approved [3,9,10]. The foundational treatment approach focuses on four key components. First, seizure control through early administration of antiepileptic drugs such as levetiracetam or phenytoin, with continuous EEG monitoring recommended for refractory cases. Second, intracranial pressure

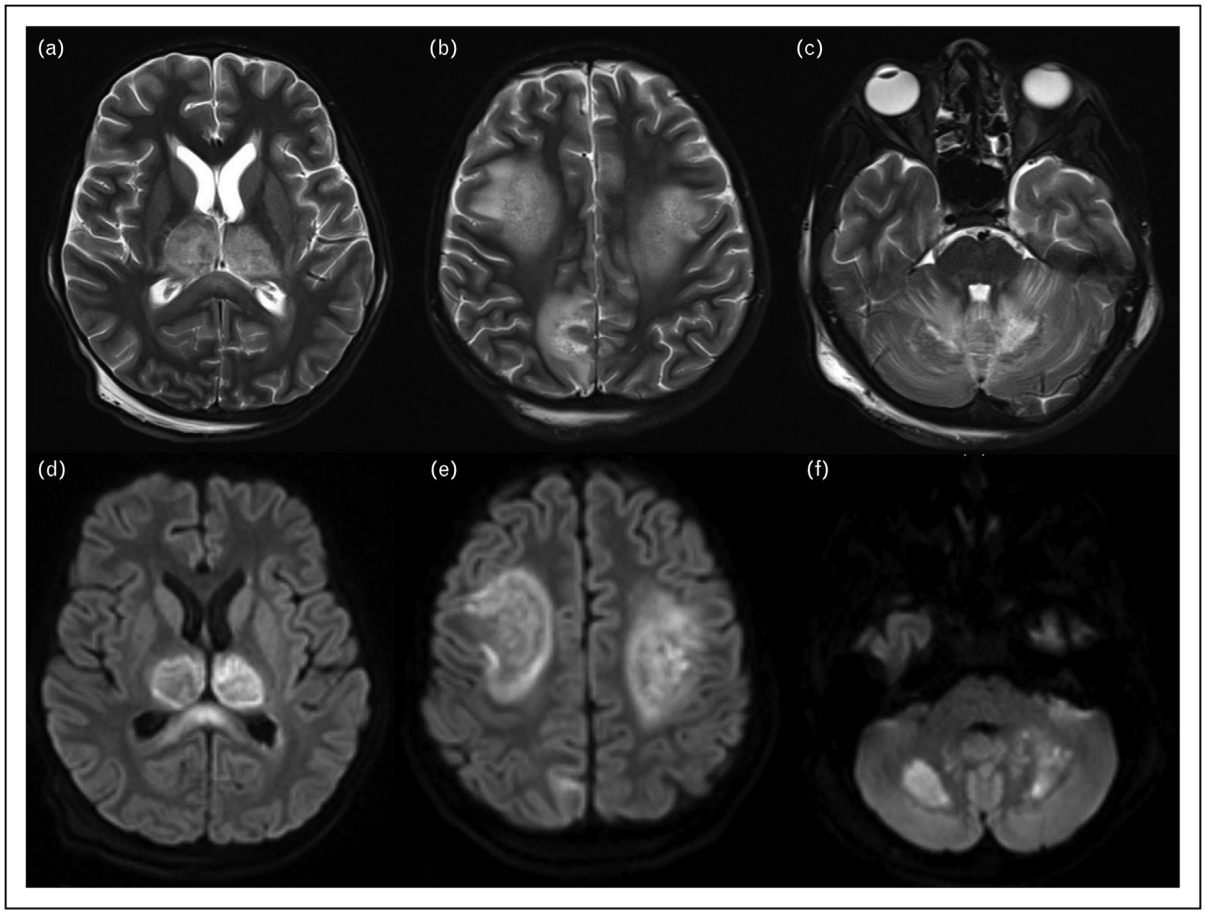

FIGURE 1. Aute necrotizing encephalitis in dengue. (a–c) MRI showing T2 Fluid Attenuated Inversion Recovery (FLAIR) sequence showing hyperintensities involving: (a) bilateral thalamus, (b) bilateral subcortical white matter involving the frontal and parietal lobes, (c) cerebellum; (d–e) corresponding areas in diffusion-weighted imaging showing hyperintensities suggestive of vasogenic oedema.

management employing 30° head elevation, osmotic therapy using mannitol or hypertonic saline, and controlled hyperventilation in severe cases. Third, careful fluid and electrolyte management through balanced crystalloid infusion guided by hemodynamic monitoring to prevent both hypovolemia and fluid overload. Fourth, comprehensive systemic support, including vigilant organ function monitoring and appropriate haematological support when clinically indicated.

Several investigational antiviral strategies are currently being explored based on our growing understanding of dengue neuropathogenesis. Among direct-acting antivirals, Balapiravir (a nucleoside analogue) demonstrated viral load reduction in phase I trials, though its efficacy specifically for neurological complications remains unproven [29,54]. Celgosivir, an alpha- glucosidase inhibitor, shows promise in inhibiting viral maturation in preclinical models [55], whereas JNJ-1802, an NS4B inhibitor currently in phase II trials, has demonstrated activity against all four dengue serotypes [56]. VIS513 (anti-E protein mAb) neutralizes all serotypes in monoclonal antibody therapies and has shown BBB penetration in primate models [57,58]. In murine studies, the 2B7 antibody targeting NS1 reduces endothelial dysfunction and vascular leakage [59], and DENG-3, a humanized monoclonal antibody cocktail, is in development for both treatment and prophylaxis purposes [60].

Immunomodulatory approaches are being actively investigated due to the prominent inflammatory cascade in dengue encephalitis. According to observational studies, corticosteroids, particularly methylprednisolone at 10–30 mg/kg/day for 3–5 days, have shown potential benefit in severe dengue with CNS involvement [61,62]. Intravenous immunoglobulin (IVIG) at 1–2 g/kg over 2–5 days may help mitigate ADE effects [63,64]. Emerging cytokine-targeted therapies, including anti-IL-6 (tocilizumab) and anti-TNF-α (infliximab), are being evaluated in refractory cases, while CXCL10 inhibitors show promise in preclinical models for reducing neuroinflammation [65].

DENGUE ACUTE NECROTIZING ENCEPHALOPATHY

Dengue acute necrotizing encephalopathy (ANE) is a rare but severe neurological complication of dengue infection, characterized by rapid-onset encephalopathy, seizures, and multifocal brain lesions [66,67]. Radiology reveals symmetric lesions in the thalamus, brainstem, and cerebral white matter. This clinical picture is seen with other flaviviral illness as well. The pathogenesis is thought to involve a 'cytokine storm' triggered by dengue virus infection, leading to BBB disruption, endothelial damage, and subsequent haemorrhagic necrosis [68▪▪].

Diagnosis requires neuroimaging (MRI showing characteristic symmetric thalamic lesions with haemorrhage), CSF analysis with a lymphocytic pleocytosis suggestive of a viral meningoencephalitis and a positive dengue serology [69]. Treatment remains supportive, including intensive care management, seizure control, and measures to reduce intracranial pressure. Despite limited evidence, immunomodulatory therapies (steroids, IVIG) have been attempted. Prognosis is often poor, with high mortality or severe neurological sequelae in survivors. Early recognition and aggressive, supportive care are crucial [68▪▪,69]. Further research is needed to understand the exact mechanisms and develop targeted therapies for this devastating complication of dengue infection.

DENGUE VACCINES

Currently, two Dengue vaccines have been licensed for clinical use: CYD-TDV (Dengvaxia, Sanofi, Paris, France) and TAK-003 (Qdenga, Takeda Pharmaceutical Company Limited, Tokyo Japan) [70,71]. Dengvaxia is a live-attenuated vaccine combining four monovalent chimeric vaccine viruses, namely CYD-1 and CYD-4. The backbone is the yellow fever virus 17D vaccine vector, where the genes encoding prM and E proteins of the yellow fever virus have been replaced by the corresponding genes from DENV-1 to DENV-4. Dengvaxia provides 76% efficacy in seropositive individuals aged 9 years and above significantly reducing severe dengue and hospitalization with varying efficacy across serotypes (i.e. approximately 50% for DENV-1, 42% for DENV-2, 74% for DENV-3, and 78% for DENV-4), whereas vaccination in seronegative individuals shows only 38.8% efficacy and an increased risk of severe dengue [71,72]. However, there were reports of serious adverse events in children, especially those who were seronegative at the time of vaccination, had recurrent hospitalizations with severe dengue, with fatalities indicating a possible 'vaccine-induced' enhancement [73]. Hence, it is currently recommended for administration only to seropositive individuals [74].

TAK-003 is a live-attenuated tetravalent vaccine based on a DENV-2 backbone. In an exploratory study to assess vaccine efficacy, among 13 380 participants receiving at least one dose of vaccine, the vaccine efficacy against virologically confirmed dengue (VCD) was 82.1% [75]. It has demonstrated long-term efficacy and safety against DENV-1 to DENV-4 in previously exposed individuals. In naive individuals, this observation was limited to serotypes DENV-1 and DENV-2 [76▪].

Butantan-DV is a live-attenuated vaccine developed by the National Institute of Health (NIH) and is currently undergoing a phase 3 trial with a 5-year planned follow-up. This is a single- dose, live-attenuated vaccine composed of all four serotypes of Dengue on an attenuated DENV-4 backbone. Two-year follow-up data revealed 89.5% efficacy against symptomatic DENV- 1 infection and 69.6% efficacy against symptomatic DENV-2 infection, irrespective of baseline serostatus [70].

A potentially safer vaccine, DSV-4, which does not exhibit ADE, is under development. This is a subunit vaccine containing HBsAg and a second protein, DS, co-assembled into mosaic virus-like particles (VLPs) [74].

FUTURE DIRECTIONS AND RESEARCH GAPS

Treatment in early Dengue is likely to be benefitted by antivirals with response monitored by quantitative PCR in the blood. However, severe dengue manifestations occur late in the course of illness and are presumed to be due to the host immune response. Immunomodulators are likely to be useful in this stage of illness. However, data with numerous therapeutic candidates have been disappointing suggesting that significant evidence gaps challenge optimal treatment. There is limited clinical trial data specifically addressing neurological manifestations, coupled with heterogeneity in case definitions and outcome measures across studies. Pharmacokinetic uncertainties regarding CNS penetration of various drugs and potential risks of immunomodulation during acute infection further complicate treatment decisions. Current research priorities focus on developing consensus treatment protocols through international registries, implementing biomarker-guided therapy using CSF IL-6, CXCL10, or NS1 levels, exploring combinatorial approaches that target both viral replication and host response, and employing adaptive trial designs suitable for studying these rare neurological complications.

The therapeutic landscape is evolving from supportive management to targeted therapy, including monoclonal antibodies and immunoglobulins. Although current management remains predominantly symptom-based, emerging evidence supports the potential benefit of combining antiviral agents with immune modulation strategies. Future treatment paradigms will likely incorporate early antiviral administration in high-risk cases, selective immunomodulation guided by cytokine profiles, adjunctive neuroprotection strategies, and personalized approaches informed by host genetic factors. Multicentre collaborative studies from varying ethnicities are imperative to better inform therapeutic modalities and management strategies for CNS complications in dengue. These efforts will be crucial for improving outcomes in this challenging condition that poses significant public health threats in endemic regions worldwide.

CONCLUSION

The findings of this review emphasize the critical need for heightened awareness and understanding of dengue encephalitis among healthcare professionals. Given the increasing incidence of dengue worldwide and its potential neurological complications, early recognition and diagnosis are paramount to improving patient outcomes. MRI findings such as T2 hyperintensities, thalamic lesions, and microhaemorrhages serve as essential indicators for diagnosing NeuroDengue. However, the nonspecific nature of these imaging results highlights the necessity for comprehensive diagnostic procedures, including CSF PCR testing for definitive identification of the virus and evaluation of neuroinflammatory markers. Moreover, the understanding of the inflammatory response in dengue encephalitis, illustrated by elevated levels of IL-6 and TNF-α in CSF, strengthens the rationale for early intervention and tailored management strategies. Although supportive care remains the cornerstone of treatment, the potential benefits of adjunct therapies such as IVIG and corticosteroids in select patients warrant further investigation.

In summary, recognizing the serious implications of dengue encephalitis is vital in clinical practice, especially as the global burden of the disease continues to escalate. Enhanced diagnostic capabilities and a solid understanding of the pathophysiology can lead to timely and effective management strategies, ultimately reducing morbidity and mortality associated with this severe complication of dengue infection. Continuous research efforts are necessary to clarify the various nuances involved in the impact of dengue-related neurological syndromes and develop targeted therapies to mitigate the same.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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