Neurological Complications of Dengue Fever

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Abstract
Purpose of Review To discuss the neurological complications of dengue virus (DENV) infection and their pathogenesis.

Recent Findings Include recognition of the four different serotypes of DENV and their epidemiology as well as recognition of the expanded dengue syndrome encompassing multisystem involvement in the severe form of the disease including involvement of the central nervous system (CNS). DENV is a neurotropic virus with the ability to infect the supporting cells of the CNS. Neural injury during the acute stage of the infection results from direct neuro-invasion and/or the phenomenon of antibody-dependent enhancement, resulting in plasma leakage and coagulopathy. Immune mechanisms have been implicated in the development of the delayed neurological sequelae through molecular mimicry. A myriad of neurological syndromes has been described as a result of the involvement of the CNS, the peripheral nervous system (PNS), or both.

Summary Neurological manifestations in DENV infection are increasingly being recognized, some of which are potentially fatal if not treated promptly. DENV encephalopathy and encephalitis should be considered in the differential diagnosis of other acute febrile encephalopathies, autoimmune encephalitides, and in cases of encephalopathy/encephalitis related to SARS-CoV2 infection, especially in dengue-endemic areas. Acute disseminated encephalomyelitis (ADEM) may be occasionally encountered. Clinicians should be knowledgeable of the expanded dengue syndrome characterized by the concurrent compromise of cardiac, neurological, gastrointestinal, renal, and hematopoietic systems. Isolated cranial nerve palsies occur rather uncommonly and are often steroid responsive. These neuropathies may result from the direct involvement of cranial nerve nuclei or nerve involvement or may be immune-mediated. Even if the diagnosis of dengue is confirmed, it is absolutely imperative to exclude other well-known causes of isolated cranial nerve palsies.

Keywords Dengue virus · Dengue hemorrhagic fever · Dengue shock syndrome · Neurological complications of dengue

Introduction

Dengue is the second most common mosquito-borne disease affecting human beings after malaria [1••]. There are four closely related but antigenically different virus serotypes: DENV1 to DENV4. Transmitted by mosquitoes of the genus Aedes, clinical manifestations range from an asymptomatic state to a severe hemorrhagic fever.

In 2009, the WHO released new dengue guidelines and a new classification, which included CNS involvement in the definition of severe disease [1••]. A change in the spectrum of clinical manifestations has been recently noted with neurological manifestations being recognized more frequently [2••,
The incidence of encephalopathy and encephalitis, the most common neurological complications of dengue, has been estimated to be between 0.5 and 6.2% [2••, 5].

Neurological manifestations of DENV have been reported from many countries distributed on all continents. Affected subjects range from the very young (3 months of age) to older individuals (60 years) [4••, 5, 6]. High body temperature, elevated hematocrit, thrombocytopenia, skin rash, and liver dysfunction are independent risk factors for the neurological complications of DENV infection [6]. The various neurological manifestations reported include encephalitis, myelitis, Guillain–Barré syndrome (GBS), and myositis. Such manifestations are mainly associated with DENV-2 and DENV-3 infections. These serotypes have been found in cases of encephalitis, meningitis, and myelitis [7, 8••, 9]. DENV-4 has also been detected in brain cells by immune-histochemistry and in the CSF of patients with encephalitis [10, 11•].

CNS complications have been attributed to the multisystem derangement caused by the DENV, leading to encephalopathy [2••, 3••, 4••, 5, 6, 7, 8••]. Although the DENV was initially considered a non-neurotropic virus, neuro-invasion has been demonstrated by detection of DENV antigen in the brain by immune-histochemistry in fatal cases of dengue encephalopathy [10] and also by polymerase chain reaction (PCR) and IgM antibody tests in CSF among patients with dengue encephalitis [11•].

**Epidemiology**

The worldwide occurrence of dengue has increased in recent times with about half of the world’s population being at risk. Of the estimated 100–400 million infections occurring each year, over 80% are generally mild or asymptomatic. Hence, the actual number of dengue cases tends to be under-reported [12, 13, 14••]. Many cases are also misdiagnosed.

One modeling estimates 390 million dengue virus infections per year (95% confidence interval 284–528 million), of which 96 million (67–136 million) manifest clinically with any severity of the disease [15]. Despite a risk of infection occurring in 129 countries, 70% of the actual burden exists in countries in Asia [16•]. The WHO reported an increase in the number of dengue cases of over 8-fold in the last two decades, from 505,430 cases in 2000 to over 2.4 million in 2010 and 5.2 million in 2019 [17••]. Reported deaths between the year 2000 and 2015 increased from 960 to 4032, mostly affecting young subjects [17••]. The total number of cases seemingly decreased during the years 2020 and 2021, as well as for reported deaths. However, the data are not yet complete, and the COVID-19 pandemic might also have hampered case reporting in several countries.

Potential reasons for the global resurgence and spread of dengue fever include population explosion, uncontrolled urbanization in tropical and subtropical countries with poor sanitation, unreliable water supply systems, poor solid waste disposal, increase of non-bio-degradable containers in endemic areas resulting in the proliferation of breeding sites for Aedes mosquitoes, lack of effective mosquito control programs, and human traveling [18]. The rapid evolution of dengue viruses with more virulent genotypes may also be contributing to the rapid spread of the infection [19••]. Around half a million people with severe dengue require hospitalization every year, a very large proportion of whom are children. About 2.5% of those affected die [20]. The estimated global mortality rate is 25,000 patients annually [20]. A change in serotypes of prevalent DENV has resulted in major dengue epidemics [21]. In Asian countries, the predominant serotype of DENV-2 has now been replaced with DENV-3 [21].

**Dengue Viruses and Vectors**

DENVs are single-stranded RNA viruses, members of the *Flaviviridae* family, genus *Flavirus*. The RNA genome is composed of seven non-structural protein genes (NS) and three structural protein genes called core, membrane, and envelope, respectively [22••] [DENV-1 to DENV-4]. Several genotypes from each of these serotypes with varying degrees of virulence have been described. All four DENV serotypes can circulate simultaneously in endemic tropical and subtropical countries and in both urban and semi-urban environments [23, 24, 25].

Humans are the unique reservoir hosts except for some rural areas in Southeast Asia and West Africa, where non-human primates may also be affected. Viral amplification occurs in humans during the viremic phase, with mosquitoes becoming infected when they bite people during this time. The extrinsic incubation period is the period between the time when the mosquito takes an infected blood meal and the time when the mosquito itself becomes infectious. This extrinsic incubation period for dengue is temperature-dependent, and only at the end of this period do mosquitoes have the virus in their salivary glands and can infect and transmit the virus to other people when they are bitten. Once infected, mosquitoes remain infective for their average life span (30–45 days) and can transmit the virus to their progeny through a trans-ovarian route [26].

Aedes mosquitoes, namely *Aedes aegypti*, *Aedes albopictus*, *Aedes scutellaris*, and *Aedes polynesiensis*, are the recognized vectors for the transmission of dengue infection. *Aedes aegypti*, the most important vector, originated in Africa and subsequently spread to tropical and subtropical areas following international trade. *Aedes polynesiensis* and *Aedes scutellaris* are commonly found in South Pacific regions.
Aedes albopictus, originally from Southeast Asian forests, has adapted to urban and semi-urban environments [27]. Aedes albopictus, in recent times, has also spread from Asia to other continents through the international trade of used tires; mosquito-deposited eggs remain viable for many months even in the absence of water collections. As the species (Aedes Albopictus) can adapt to cold temperatures and feed on other animals and birds, they can survive far from human dwellings. Thus, Aedes albopictus is proving to be an emergent health challenge for the transmission of DENV in temperate regions including some Eastern European and Mediterranean basin countries [27].

Pathogenesis

As stated, dengue may result from any one of four serotypes, namely DENV1 to DENV4. An infection caused by one of them can cause dengue fever. The infection provides life-long protective immunity to the same subtype, but not to infections from other serotypes [28]. History of the previous infection with a different serotype increases the chances of developing dengue hemorrhagic fever in subsequent infections with viruses of other serotypes. This curious and paradoxical phenomenon is known as the “antibody-dependent enhancement” (ADE) [29], where heterotypic non-neutralizing antibodies form complexes with DENV infecting mononuclear phagocytes with enhanced efficiency. Consequently, a higher number of host cells become infected, enhancing viral replication, with worsening of clinical signs. All of these may contribute to the development of neurological and other complications [29•]. A different type of problem may be envisaged to occur with ADE in the current times of the SARS-CoV2 pandemic [29, 30••].

Endothelial dysfunction leading to vascular leakage and increased permeability is the hallmark of severe dengue manifested as shock and encephalopathy [31••, 32•]. Although this may lead to serious consequences, often rapid and complete reversal occurs, suggesting this to be likely due to inflammatory mediators, rather than infection of the endothelium. Several factors may be involved [31••]. Cytokines such as tumor necrosis factor-a (TNF-a), often elevated in the critical phase of dengue, are likely candidates. Dengue NS1, a soluble non-structural viral protein, can also disrupt the endothelial glyocalyx, thus contributing to vascular leakage. Some discordance between the timing of NS1 antigenemia and the occurrence of manifestations of vascular leakage may point against this hypothesis. Additionally, levels of several inflammatory lipid mediators like platelet-activating factor (PAF) and leukotrienes are raised during the acute phase of the disease. Moreover, vascular endothelial growth factor and angiopoietin-2 levels are elevated in patients with dengue hemorrhagic fever, and these tend to induce the activity of phospholipases involved in the generation of PAF. Platelets may also contribute to endothelial dysfunction by the production of interleukin-1b and inflammatory cytokines by the monocytes. Thus, drugs that block the downstream immunological cascade may have some beneficial role in the treatment of the severe forms of the disease. In addition, a structural compromise in the integrity of the endothelial glyocalyx layer (EGL) seems to occur [32•]. Although the exact mechanism of EGL degradation in dengue is unknown, EGL degradation has been linked to coagulation disorders, increased leukocyte adhesion to the endothelium, and fluid extravasation, which are associated with increased plasma leakage.

Neuro-pathogenesis

The neuro-pathogenesis of DENV infection remains poorly understood. Both viral and host factors probably play important roles in the genesis of dengue-related neurological syndromes. Three mechanisms may be operative: direct CNS invasion by the virus, autoimmune reactions, and metabolic alterations.

Although DENV has traditionally been considered to be non-neurotropic, neurological involvement, demonstration of CSF viral particles, and damage to the BBB, all seem to be suggestive of direct viral neurotropism [33••].

Recent studies have suggested the role of neuroinflammation in dengue [28, 33••, 34••]. The non-structural 1 antigen (NS1Ag) is a secreted glycoprotein that functions as a cofactor for viral RNA replication and triggers cytokine release. The natural killer cells are actively involved in the pathogenesis of neurological manifestations as evidenced by their early activation, and subsequently, these cells activate T helper (Th) cells. These Th cells divide and transform into Th17 and Th9 cells and promote the further release of pro-inflammatory cytokines like interferon-gamma, interleukin (IL) 12, IL-4, and transforming growth factor-beta. These cytokines further damage the blood–brain barrier (BBB) and subsequently facilitate the entry of other immune mediators into the brain resulting in neuroinflammation [28].

Earlier, the neurological complications of DENV infection were classified into three categories based on pathogenesis [35•, 36]: [1••] those caused by metabolic disturbance, e.g., encephalopathy; [2••] those caused by the viral invasion, including encephalitis, meningitis, myositis, and myelitis; and [3••] those caused by autoimmune reactions, including ADEM, optic neuritis, myelitis, and GBS.

More recently, Solbrig and Perng reported three classes of neurological involvement: those of the CNS and eyes, those associated with PNS syndromes, and those occurring in the convalescent stage or post-dengue immune-mediated syndromes [37••].
Clinical Spectrum

The 2009 World Health Organization (WHO) classification [1••] grouped dengue infection into three categories, including dengue with no warning signs, disease with warning signs, and severe dengue. This revised classification includes CNS involvement as a manifestation of severe dengue.

Dengue Without Warning Signs

A presumptive diagnosis is made in the setting of residence in or travel to an endemic area plus fever and any two of the following [1••]:

- nausea/vomiting
- rash
- headache, eye pain, muscle aches, or joint pain
- leukopenia
- positive tourniquet test

Dengue with Warning Signs

Dengue with warning signs of severe infection includes dengue infection as defined above in addition to any of the following [1••]:

- abdominal pain or tenderness
- persistent vomiting
- clinical fluid accumulation (ascites, pleural effusion)
- mucosal bleeding
- lethargy or restlessness
- hepatomegaly >2 cm
- increase in the hematocrit concurrent with a rapid decrease in the platelet count

Severe Dengue

It includes dengue infection with at least one of the following [1••]:

- severe plasma leakage leading to
  - shock
  - fluid accumulation with respiratory distress
- severe bleeding (as evaluated by a clinician)
- severe organ involvement
  - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1000 units/L
  - impaired consciousness
  - organ failure

Expanded Dengue Syndrome

The expanded dengue syndrome (EDS) refers to those manifestations involving multiple organ systems in cases of dengue fever [38••]. Certain high-risk groups such as pregnant women, infants, the elderly, patients with coronary artery disease, hemoglobinopathies, and immune-compromised individuals are particularly susceptible to developing EDS [38••, 39••, 40••]. Multi-organ involving features (neurological complications discussed separately) include the following.

- cardiac: sinus bradycardia or tachycardia, atrio-ventricular block, sino-atrial exit block, ventricular bigeminy and/or trigeminy, paroxysmal supraventricular tachycardia, atrial fibrillation, myocarditis, pericarditis, and pericardial effusion
- gastrointestinal: acute liver failure, acalculous cholecystitis, acute pancreatitis, and bleeding gastric ulcers
- renal: acute kidney injury
- respiratory: adult respiratory distress syndrome, pneumonia/bronchiolitis, and pulmonary hemorrhages
- hematological: splenomegaly, hemophagocytic lymphohistiocytosis, aplastic anemia, and thrombotic thrombocytopenic purpura

Neurological Complications

The newer classification of neurological involvement with dengue infection aims at disentangling dengue-associated involvement of CNS and eyes, involvement of the PNS, and convalescent or post-dengue immune-mediated syndromes [40••].

CNS involvement may occur in all three categories: dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. For the diagnosis of any neurological disorder attributed to DENV infection, a confirmed diagnosis of DENV infection, as defined by the WHO, is essential. This includes any one of the following: PCR positivity, virus culture positivity, IgM sero-conversion in paired serum samples, or four times IgG titer increase in paired serum samples [1••]. CNS involvement by dengue is characterized by any one of the following: impaired level of consciousness (for children <5 years of age, Blantyre coma score < 4; and for children ≥5 years of age, Glasgow coma Score <14), neck stiffness, focal neurological signs, or seizures [1••].

Dengue Encephalopathy

Encephalopathy is the most commonly encountered neurological complication associated with DENV infection. Dengue encephalopathy may result from systemic infection and may be precipitated by anoxia, cerebral edema,
hyponatremia, prolonged shock, systemic hemorrhage, acute liver or renal failure, or the release of toxic substances [40].

Dengue encephalopathy was earlier considered to be exclusively associated with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). In a 2-year prospective case-control study performed in Vietnam, dengue-associated encephalopathy accounted for 0.5% of 5400 serologically confirmed patients admitted with DHF [41].

Burst suppression, electrographic seizures, focal patterns, or Epilepsia partialis continua may be observed on EEGs in these patients [42].

The CSF profile is usually normal in cases of dengue encephalopathy. Neuroimaging studies may be normal or show diffuse cerebral edema [43].

Recent research suggests that in dengue virus infection, cytokine overproduction results in immune-mediated endothelial cell damage which contributes to many of the CNS manifestations. Cytokines like IL-1β, TNF, IL6, IL8, IL10, enzymes like MMP2, and chemotactic proteins like IP2 and RANTES (regulated upon activation, normal T cell expressed, and secreted; also known as CCL5) play an upper hand in causing endothelial injury and dysfunction leading to increased vascular permeability and fluid leakage [31, 32]. This leakage may result in generalized cerebral edema.

Treatment outcome for patients with dengue encephalopathy is variable and depends on causal/precipitating factors as well as on the extent of medical care. Without supportive treatment, mortality can be quite high. In one report of 15 patients with dengue encephalopathy from Sri Lanka (all with DSS), there were seven fatalities. Contributing factors to encephalopathy included acute liver failure (11 cases), electrolyte imbalance (12 cases), and shock (6 cases) [44].

**Dengue Encephalitis**

In the last ten years, the full spectrum of brain injury due to CNS invasion and neurotropic effects of the dengue virus has been unraveled. Reduced levels of consciousness, headache, fever, nausea and vomiting, seizures, focal neurological deficits, and behavioral symptoms may be observed in patients with dengue encephalitis [45]. The usual symptoms of dengue fever like rashes, muscular pains, and bleeding are generally not seen in more than 50% of patients with encephalitis [46]. DENV-related encephalitic syndrome may be best diagnosed by the combined use of PCR and immunological tests in serum/CSF.

Dengue encephalitis may be characterized by altered levels of consciousness or personality and/or seizures and/or focal neurological signs, reactive IgM dengue antibody, NS1 antigen or positive dengue PCR on serum and/or CSF, exclusion of other causes of viral encephalitis, or encephalopathy [47, 48].

A head CT scan often shows hyperdense parenchymal foci representing spontaneous microhemorrhages as well as hypodensities in the thalamus and basal ganglia (Fig. 1). Brain MRI plays an important role in identifying the exact anatomical areas of involvement and substantiating a diagnosis of dengue encephalitis in patients with neurological manifestations mentioned earlier [3]. Commonly affected regions include the basal ganglia, thalamus, temporal lobes, hippocampus, cerebellum, and cerebral white matter, where T2 sequences may demonstrate hyperintensities. Rather uncommonly, similar lesions can be found in the brainstem (particularly the substantia nigra) and cerebellum. DWI/ADC images may demonstrate areas of restricted diffusion in most cases. In SWI images, microhemorrhages are commonly demonstrated. Symmetric gyral edema and altered signal intensities involving bilateral temporal perisylvian regions, hippocampi, and cingulate gyri have been reported [49]. Meningeal enhancement on post-contrast MRI may be seen occasionally [43].

The differential diagnoses for the above-mentioned imaging findings include ADEM, Japanese B encephalitis, and Chikungunya [49, 50].

A definitive diagnosis of CNS affection by DENV may be challenging. While detection of dengue NS1 antigen, DENV, and DENV-specific IgM antibodies in the CSF are helpful in confirming the diagnosis of dengue encephalitis, the sensitivity of this test is rather low. Similarly, the yield of PCR studies may also be low due to a lower CSF viral load. Hence, in most cases, the diagnosis of dengue encephalitis is somewhat made indirectly and based on (a) clinical suspicion of dengue, (b) confirmation of systemic DENV infection by NS1 antigen early in the disease, (c) confirmation by DENV-specific IgM in serum, (d) development of an

![Non-contrast head CT of a 22-year-old man with DENV encephalitis shows hypodensities in both thalami and brain stem (reprinted from the literature [3]: case 1.2.1 with permission of publishers)](image)
encephalitic syndrome with or without abnormal CSF study, and finally (e) with an abnormal brain imaging.

**Differentiation of Dengue Encephalitis and Japanese Encephalitis**

Japanese encephalitis virus (JEV) is a proven neurotropic virus which mainly targets cerebral neurons [51••]. Nearly 75% of symptomatic patients with JE show manifestations of encephalitis, which often account for case fatality [52•, 53]. The cellular apoptosis in JE is much more widespread, involving neurons, microglia, and endothelial cells with the development of brain edema than what is seen in DENV infection [54]. As a result, up to one-third of JE cases who were hospitalized died, while about one-half of all survivors showed permanent neurological sequelae [55]. In contrast, most patients, even with neurological manifestations in dengue infection, recover well with no very significant residual deficits.

**Ocular Manifestations**

Ocular involvement is currently being recognized more frequently and studied more thoroughly due to the availability of ocular coherence tomography (OCT) and infrared fundus photography. The ocular involvement described so far includes maculopathy, blurred vision, scotoma, floaters, subconjunctival hemorrhages, uveitis, vitritis, retinal hemorrhages, retinal venular widening, higher retinal vascular dimension, retinal vascular sheathing, retinal pigment epithelium mottling, tortuous vessels, acute macular neuroretinopathy, macular, intra-retinal edema, cotton wool spots, Roth’s spot, retinal detachment, retinochoroiditis, neuroretinitis, choroidal effusions, choroidal neovascularization, optic disc swelling and neuritis, oculomotor nerve palsy, and panophthalmitis [3••, 56, 57].

In general, symptoms of ocular involvement are suggested by visual loss, ocular pain, redness, metamorphopsia, impaired color vision, diplopia, eye flashes, haloes, and photophobia. Lesions located in the peripheral retina may be asymptomatic and difficult to visualize. Hence, ocular involvement in dengue is often under-reported [57].

The exact pathogenetic mechanisms for all the ocular manifestations are not fully understood. While thrombocytopenia may be contributory to the hemorrhagic lesions, there are indeed other plausible factors. Some suggested dengue-associated vasculopathy, pro-inflammatory cytokines, and immune mechanisms [58]. Hemorrhages associated with dengue-related maculopathy are mostly intra-retinal and can take the form of dots, blots, or flame-shaped hemorrhage [59••]. Vascular sheathing and vasculitis are often found in association with macular hemorrhage [60]. Dengue-related foveolitis refers to the yellow-orange lesion at the fovea of patients with dengue maculopathy, and this can be detected by OCT. [61] Macular edema is a common presentation of dengue-related maculopathy. On OCT, different varieties of macular edema can be recognized [62]. Hyperemic swollen optic discs with peri-discal hemorrhages are common presentations of dengue-related optic neuropathy. The intrinsic pathology in the affected optic nerves is unknown, but it is likely to be different from that encountered in demyelinating optic neuritis [63]. Central serous chorio-retinopathy is a poorly understood phenomenon and is more so when it occurs in dengue viral infection. Several factors like stress related to a viral infection, catecholamine release, steroid therapy, and genetic factors may be operative in its generation [64•].

Most dengue-related ocular conditions resolve spontaneously. Steroids may be helpful when an autoimmune mechanism is suspected, but they should be avoided in the stage of acute viremia (Fig. 2).

**Dengue-associated Stroke**

Stroke associated with DENV infection may be ischemic or hemorrhagic [3••, 65, 66••].

A. Ischemic strokes: These may occur as watershed infarctions, cortical infarctions, and lacunar infarctions.

B. Hemorrhagic strokes: These may take the form of basal ganglia hemorrhage, lobar hemorrhage (single or multiple), cerebellar hemorrhages (may be bilateral), pontine hemorrhage, subdural hematoma (acute-unilateral or bilateral), pituitary apoplexy (hemorrhagic), and subarachnoid hemorrhages (generally non-aneurysmal).

The proportion of hospitalized, confirmed dengue patients who suffer a hemorrhagic stroke ranges from 0.26% (India) [67] to as low as 0.06% (Brazil) [68].

Presentation is often with fever, moderate-to-severe headaches, vomiting, sudden hemiparesis, and impaired level of consciousness. Patients may not have visible bleeding from other sites except intracranial bleeding. Hemorrhages may be caused by elevated vascular permeability, plasma leakage, and vasculitis [69•].

Most patients have intracranial bleeding a week after fever onset [66••]. Basal ganglia hemorrhages and multiple lobar hemorrhages have been described [68]. Less common clinical forms of intracranial bleeding include [70, 71, 72, 73] bilateral cerebellar hemorrhages, pontine hemorrhages, acute subdural hematoma, multiple acute subdural hematomas, pituitary apoplexy, subarachnoid hemorrhage, and focal subarachnoid hemorrhage associated with transient thrombocytopenia.

The platelet count does not always correlate with the occurrence of ICHs, thus raising the possibility of an interplay of multiple factors such as vasculopathy,
coagulopathy, and platelet dysfunction [73]. The presence of CSF immune markers in the CSF suggests a breakdown of the BBB and blood-CSF barrier in patients with severe dengue. The NS1 antigen may also activate the conversion of plasminogen to plasmin and thereby induce fibrinolysis. There are no evidence-based guidelines for the management of dengue-related intracranial hemorrhage.

Cases of dengue fever with thrombocytopenia and ischemic stroke are possible but infrequent [74]. Head CT and brain MRI should be done to confirm the clinical suspicion of stroke. Several areas of watershed infarctions, small cortical infarctions, corona radiata, and putaminal infarctions have been reported [75••]. Gradient-echo MRI can detect microbleeds, and diffusion-weighted images (DWI) can demonstrate acute and subacute infarctions.

**Posterior Reversible Encephalopathy Syndrome**

This condition is rarely observed in dengue and detectable on MRI, especially on T2 and FLAIR sequences [76, 77, 78••]. Bilateral cortical visual loss may be demonstrable in conscious patients or upon regaining consciousness during the recovery stage. Its pathogenesis seems to be somewhat different from those encountered in hypertensive emergencies like eclampsia or pre-eclampsia. Posterior reversible encephalopathy syndrome (PRES) associated with dengue virus infection is more of cytotoxic origin than vasogenic. Endothelial damage appears to play a major role in the genesis of PRES in dengue, and this may account for its reversibility in control of the infection [78••] (Fig. 3a,b). Platelet activation and secretion of platelet-activating factor and release of NO are other implicated pathologic mechanisms.

**Immune-mediated Neurological Syndromes**

The various immune-mediated neurological syndromes described in association with DENV infection include mononeuropathies, GBS, brachial neuritis, transverse myelitis, ADEM, acute cerebellitis, opsoclonus-myoclonus syndrome, and Parkinsonism [4••, 8••, 28, 40••]. Post-dengue

![Fig. 2 (A) Brain MRI (T2 sequence) of a 16-year-old adolescent girl with dengue fever who presented with seizures, right hemiplegia, and altered sensorium, showing a large left parietal intracerebral hemorrhage. She also complained of visual blurring of the right eye and ophthalmoscopy demonstrated macular edema with star formation (B) (reprinted from the literature [3••]; case 1.2.7 with permission of publishers)
immune-mediated neurological syndromes usually resolve within weeks or a few months.

**Mononeuropathies**

Involvement of cranial nerves following dengue fever includes optic neuritis, oculomotor nerve palsy, isolated sixth nerve palsy, isolated Bell’s palsy, long thoracic neuropathy, and isolated phrenic nerve palsy [79, 80, 81]. Diagnosis is usually one of exclusion. The likely pathogenetic mechanism appears to be immune-mediated. Treatment is mostly supportive. Corticosteroids may be helpful if prescribed early in the course.

**Guillain-Barré Syndrome and Variants**

Polyradiculoneuropathies, lumbosacral plexopathies, GBS, and GBS variants have been associated with DENV infection [82, 83, 84, 85, 86, 87, 88•, 89•, 90]. GBS may occur early in the course of the illness or may be delayed. The exact pathogenetic mechanism is unclear, but it is highly likely that this is an immune-mediated disorder, as immunoglobulins evoked by dengue infection cross-react with peripheral nerve components, which share cross-reactive epitopes [40••]. This immune response can be directed toward the myelin or axons, resulting in both a demyelinating or axonal type of polyneuropathy [90].

**Acute Transverse Myelitis**

Dengue-associated acute transverse myelitis is extremely rare. It can occur during or after the infection. Long segment involvement is the rule. The pathogenesis is thought to be immune-mediated in the post-infectious stage and as a result of direct virus invasion in the para-infectious stage [91, 92]. No cases with associated optic nerve involvement have been reported. Post-infectious immune-mediated myelitis usually arises within 1–2 weeks after the onset of initial symptoms, whereas para-infectious myelitis can take place within the first week of infection. Diagnostic confirmation demonstrates signal changes and spinal cord swelling on MR imaging of the spinal cord. Intrathecal synthesis of dengue virus-specific IgG antibodies in the CSF has been detected as well as isolation of viral RNA can be made [92, 93•]. Even if a temporal relationship with a recent dengue infection is established, neuromyelitis optica spectrum disorder (NMOSD) or multiple sclerosis (MS) need to be excluded by appropriate diagnostic tests.

**Acute Disseminated Encephalomyelitis**

ADEM may occur during the convalescence phase following DENV infection and DHF [94•, 95, 96, 97••, 98•, 99••]. Presenting symptoms often include seizures, altered sensorium, and focal neurological deficits. Such symptoms generally occur after remission of the febrile period. Mild CSF pleocytosis and moderate rise in protein concentration may be present in the CSF. Brain MRI studies detect white matter lesions on T2-weighted and FLAIR images in the centrum semiovale, corona radiata, corpus callosum, and thalamus. Spinal cord signal alterations can be detected mostly in the thoracic and cervical segments [94, 96]. Periventricular demyelination, macrophage influx, and perivascular infiltration of lymphocytes with hemorrhagic foci have been reported after histological examination of such lesions [100]. In Murthy’s study, its pathophysiology was considered to be a transient autoimmune reaction to myelin or some unknown
self-antigens [35•]. Pulse intravenous methylprednisolone is often effective during the active phase.

**Neuromuscular Complications**

**Dengue-associated Hypokalemic Paralysis**

Development of hypokalemic paralysis can be suspected in patients presenting with acute onset of flaccid quadriplegia without any cranial nerve palsy and without any sphincteric compromise. Demonstration of hypokalaemia is confirmatory. It is, however, mandatory that in all cases of suspected GBS, whether related to dengue or not, serum potassium level must be checked, and urine samples are sent for porphobilinogen. A serum potassium level of 3 mmol/liter or below would suggest the diagnosis of hypokalemic paralysis.

The onset of weakness generally occurs on an average between the 2nd and 5th day of fever, developing over a period of 4–24 h. In most patients, muscle stretch reflexes are usually absent or decreased [101, 102, 103••, 104, 105].

The pathogenesis of hypokalemia in dengue fever is not clear. Several mechanisms have been proposed [101, 102, 103••].

a) Excess use of intravenous fluid, especially lactate-containing solutions, may promote metabolic alkalois, which results in an intracellular shift of potassium, thereby lowering the serum level of potassium.

b) Due to redistribution of potassium within cells and extracellular fluid as a systemic effect of the infection.

c) Transient renal tubular abnormalities lead to increased urinary potassium excretion.

d) Stress-induced catecholamine release induces cellular uptake of potassium resulting in hypokalemia.

e) Hypokalemic periodic paralysis has been found to be generally associated with mutations in the alpha subunit of the L-type calcium channel gene (CACNA1A), while in some, mutations in the alpha subunit of the sodium channel gene (SCN4A) had been noted. It is highly likely that dengue-associated hypokalemic paralysis also occurs as a result of some kind of channelopathy induced or made apparent by the virus.

DENV-associated hypokalemic paralysis responds to low doses of potassium supplementation with rapid recovery without any residual deficits [105].

**Myositis**

Diagnosis of dengue myositis diagnosis is based on clinical manifestations of DENV infection, positive serum IgM for DENV, high serum creatine kinase levels, normal CSF, and exclusion of other causes [106••].

Dengue-associated myositis can be of varying severity, ranging from self-limiting mild muscle weakness to severe dengue myositis, resulting in quadripareisis and respiratory insufficiency. Fatalities had been noted in severe cases [107]. Concomitant myocarditis may complicate management [107]. In dengue-endemic areas, dengue myositis should be included in the differential diagnosis of pediatric acute onset of flaccid paralysis. Although a benign disease in children, dengue myositis needs differentiation from other causes of difficulty in walking in children by the presence of muscle tenderness on stretching, normal power with preserved deep tendon reflexes, and an elevated CPK [106••].

The pathogenesis of myositis remains unclear. The proposed mechanisms comprise direct muscular invasion by the DENV and immune-mediated destruction of muscle fibers, particularly by tumor necrosis factor (TNF) [108••, 109, 110]. Dengue myositis is histologically characterized by perivascular infiltration of mononuclear cells, mitochondrial proliferation, fat accumulation, nuclear centralization, fiber-type grouping, and/or focal myonecrosis [108••, 110, 111].

EMG findings are consistent with a myopathic pattern [111]. Fibrillations, sharp waves, and complex repetitive discharges do not occur [111]. Dengue myositis is considered a relatively benign and self-limiting disease among pediatric patients [109]. In adult patients, dengue myositis is often more severe, even leading to severe rhabdomyolysis. A persistent form of severe myositis, but responsive to corticosteroids, has been described [112••].

**Rhabdomyolysis**

Dengue-induced rhabdomyolysis likely results from cytokine-mediated damage to muscle cells. Cytokines, particularly TNF and interferon alpha, are released in response to dengue viral infection. Raised levels of cytokines result in an increase in intracellular free calcium, resulting from depletion of adenosine triphosphate (ATP) and/or by direct injury and disruption of the plasma membrane. Increased intracellular calcium level is injurious to muscle cells through activation of proteases, mitochondrial abnormalities, and excessive production of reactive oxygen species; all these chemical reactions ultimately result in muscle cell death [113••, 114]. Rhabdomyolysis may cause acute kidney injury (AKI) and life-threatening electrolyte disturbances.

**Myalgias**

Muscle pain, tenderness, and mild muscle swelling are the characteristic features, noted during the early phase of the
illness. The pain commonly affects the back and proximal limb muscles, causing difficulty in walking in the absence of any weakness. It is likely that direct viral invasion of muscles occurs, and subsequently, the inflammatory changes, which occur secondary to this, result in muscle pain.

Electromyography (EMG) is usually normal, but in patients with an elevated creatine kinase, mild myopathic changes have been recorded [111]. Histopathological changes that can be seen include a mild-to-moderate perivascular mononuclear infiltrate, lipid accumulation, mild mitochondrial proliferation, few central nuclei, foci of muscle necrosis, and fiber-type grouping [110, 111]. Myalgias are often transient and self-limiting.

### Cerebellar Syndromes in Dengue

Cerebellar syndromes in association with DENV, probably as a result of a low-grade inflammatory process likely immune-mediated, may occur during the acute phase of the infection or may develop within 1–3 weeks of resolution of acute dengue symptoms [115••, 116••, 117••]. Cerebellar syndromes appear to be self-remitting [115••]. Similar syndromes may occur in association with a myriad of viral infections, and hence, these need to be excluded. The other major differential is with ADEM.

### Diagnosis

In regions and seasons with a high incidence of DENV infection, the positive predictive value of clinical criteria remains robust, particularly for illnesses meeting all criteria for dengue hemorrhagic fever (DHF) [118]. The case definition of DHF requires four diagnostic components: fever, hemorrhagic manifestations (positive tourniquet test, skin and mucosal bleeding including gastrointestinal bleeding, epistaxis, menorrhagia), thrombocytopenia (≤100,000 cells/mm³), and evidence of plasma leakage (pleural effusion, ascites, or hemococoncentration ≥20%, hypoproteinemia) [118, 119]. Dengue shock syndrome is defined as DHF with circulatory failure [118].

Early clinical presentations of dengue, Chikungunya, and Zika virus infection may be indistinguishable. If feasible, laboratory diagnostic confirmation is warranted, but often, the results are not available soon enough to guide initial clinical management.

### Laboratory Testing

Laboratory diagnosis of DENV infection is established directly by detection of viral components in serum or indirectly by serology. The sensitivity of each test depends on the time of sample collection in relation to the days since the onset of the patient’s illness. Detection of viral nucleic acid by PCR has high specificity but is more costly; serology for viral antigen has lower specificity but is more accessible and less costly.

During the first week of illness, the diagnosis of DENV infection may be established via detection of viral nucleic acid in serum by means of reverse-transcriptase PCR or via detection of viral antigen non-structural protein 1 (NS1; typically, positive during the first seven days of illness). In primary infection, the sensitivity of NS1 detection can exceed 90% in primary infections, and antigenemia may persist for several days after the resolution of fever, while the sensitivity of NS1 detection is lower (60 to 80%) in secondary infections [120, 121••, 122].

Immunoglobulin M (IgM) can be detected as early as four days after the onset of illness by lateral flow immunoassay or IgM antibody capture enzyme-linked immunosorbent assay [123]. Detection of IgM in the serum obtained from patients with a clinical syndrome consistent with the diagnosis of dengue fever is widely used to establish a confirmed diagnosis. Further evidence may be obtained through IgM sero-conversion between paired acute and convalescent-phase specimens (usually sera); a diagnosis of acute DENV infection may be established by a four-fold or greater rise in antibody titer.

The probability of IgG detection depends on whether the infection is primary or secondary. Primary dengue infection is characterized by a slow and low titer antibody response; IgG is detectable at low titer beginning seven days after onset of illness and increases slowly. Secondary dengue infection is characterized by a rapid rise in antibody titer beginning four days after onset of illness, with broad cross-reactivity [123].

Serologic tests are unreliable for the diagnosis of acute DENV infection in individuals who have been vaccinated with a dengue vaccine within the previous several months [124]. In addition, serologic diagnosis of dengue may be confounded in the setting of recent infection or vaccination with an antigenically related Flavivirus such as yellow fever virus, Japanese encephalitis virus, or Zika virus [124].

DENV infection can be established by virus isolation (culture). In general, this is not warranted as a clinical diagnostic tool since results are usually not available in a clinically meaningful time frame.

Dengue viral proteins can be detected in tissue samples using immune-histochemical staining [125••]. Liver tissue appears to offer the highest yield. A biopsy is rarely indicated in patients with suspected DENV infection.

### Dengue and COVID-19 Pandemic

The advent of infections with the SARS-CoV-2 virus in pandemic proportion worldwide has added a new perspective to the differential diagnosis of acute febrile illnesses in resource
deficient tropical countries in Asia, Africa, and South America [29, 30••, 126]. As dengue and SARS-CoV2 infection manifest several similar/overlapping clinical features in the initial stages of infection and misdiagnosis may not be very uncommon. A possible explanation for the increased number of cases of both dengue and SARS-CoV2 infections in the earlier days of the pandemic may be due to misdiagnosis related to inadequate availability of sensitive molecular genetic tests in resource-limited countries [127•]. In contrast, a report from India reported a lesser number of cases of dengue in 2020 [128]. This was most likely due to lesser surveillance and testing for dengue as attention and resources were almost entirely diverted toward controlling the COVID-19 pandemic. The lockdown might also had some effects on vector breeding and disease transmission as a consequence of social distancing. Furthermore, the occurrence of false-positive IgM for dengue has also been reported in confirmed cases of SARS-CoV2 infection [129, 130•]. An important caveat is the role of vector control and changes of DENV serotype circulating during the COVID-19 pandemic in endemic regions. Continuous dengue surveillance needs to be in place to monitor the transmission dynamics of DENV infection.

Treatment

At present, there is no specific curative treatment for dengue fever. General supportive measures include fever control, intensive hematological monitoring keeping, fluid replacement, and/or blood/platelet transfusion if needed. In children, the use of aspirin should be avoided to prevent the development of Reye’s syndrome. Judicious fluid supplementation is essential. A greater than 20% rise in hematocrit would suggest significant fluid (plasma) loss, calling for aggressive volume replacement. The WHO recommends the use of crystalloids for volume replacement [1••]. Colloids and blood transfusion may be used in unresponsive patients. It is recommended that 10 ml/kg of replacement fluid should be given for every 1% of normal body weight loss [1••], in addition to maintenance fluids by the standard weight-based protocol. Platelet transfusions may be required for severe bleeding manifestations. Electrolytes and metabolic abnormalities such as hypoglycemia, liver dysfunction, or renal function abnormality should be managed accordingly [131].

No specific treatment is available for encephalopathy or encephalitis. There is no proven value of corticosteroids or antiviral agents. Symptomatic treatment such as anti-seizure medications and mannitol or diuretics for raised intracranial pressure should be provided in an intensive care setting. The immune-mediated manifestations generally respond well to immunomodulators like high doses of corticosteroids or intravenous immunoglobulin therapy. Unfortunately, DENV infection with one serotype confers immunity against that particular serotype only for a limited period but not so for other serotypes of DENV.

Concluding Remarks

Accurate diagnosis of an acute febrile illness in a tropical or subtropical country is always challenging. Advances in immunodiagnostics methods coupled with the availability of molecular diagnostic tools have eased this challenging task to some extent. The diagnostic issue becomes more complex when acute febrile illnesses are associated with neurological features especially altered sensorium. In febrile patients with altered sensorium and positive serology for dengue, the differentiation between dengue-associated encephalopathy and dengue encephalitis may be quite challenging. While a positive brain neuroimaging study would usually be suggestive of the latter, similar changes may be encountered in several other CNS viral infections of the CNS. The altered sensorium in a DENV sero-positive patient may also be due to a stroke with an intracerebral hematoma or an expanding infarct. The common practice of examining the CSF of febrile patients with altered sensorium to exclude an underlying CNS infection must be done with caution in suspected cases of dengue fever.
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