Diagnosis and Management Neurologic Manifestations Associated with Acute Dengue Virus Infection

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Abstract

Dengue virus infection is extremely common worldwide. Neurologic involvement is not very common, but several forms of central and peripheral nervous system impairments have been described in patients with dengue. Several neurologic manifestations of dengue can be found in patients with dengue. Headache can result from systemic inflammation or meningitis. Altered sensorium occurs as a consequence of encephalitis, encephalopathy, acute demyelinating encephalomyelitis, or stroke. Paraparesis or tetraparesis can be seen as a consequence of Guillain-Barré syndrome, myositis, or hypokalemic paralysis. The early recognition of neurologic the pattern of neurologic involvement is important because some of these conditions require specific and prompt therapeutic interventions. In the present paper, we review the different forms of dengue-associated neurologic disorders and propose a practical approach to treating patients with dengue-associated neurologic symptoms.

Keywords: Dengue; Encephalitis; Acute demyelinating encephalomyelitis; Peripheral nerves; Myositis; Hypokalemic paralysis

Introduction

Dengue virus is the most important mosquito-borne viral disease in the world, affecting 50 to 100 million people yearly, with nearly 500,000 severe cases. The circulation of the four types of dengue viruses and the extremely high number of cases have contributed to an expansion of the clinical aspects of the disease. In addition to the most recognised forms of the disease, which are dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS), complications of dengue affecting specific organs and systems, such as the brain, peripheral nerves, muscles, liver, and pancreas, have recently been described [1,2].

Neurologic manifestations, other than headache, occur in approximately 4-6% of dengue cases. They have been attributed to different pathophysiological mechanisms, such as direct central nervous system (CNS) viral entry, metabolic disturbances affecting CNS function, haemorrhage, and virus-generated autoimmune reactions, leading to CNS inflammation and demyelination [3,4].

The aim of the present article is to review the clinical, diagnostic, and therapeutic aspects of the most frequent neurologic symptoms associated with dengue infection in the CNS and the peripheral nervous system (PNS) and to propose a clinical approach for patients with suspected dengue-associated neurologic manifestations.

Neurologic manifestations in dengue

Headache: Headache is a very frequent complaint, not only in outpatient clinics but also in emergency rooms [5]. Headache occurs in 97.6% of dengue patients, and its features have been previously described. The pain is most frequently described in the frontal and retro-ocular regions but has also been described in the occipital, cervical, and temporal regions. Headache associated with dengue is always bilateral. Most patients complain of throbbing headaches, although some patients complain of pressing/tightening pain. The intensity of the pain is severe in almost all patients. Associated symptoms, such as nausea/vomiting, photophobia, and phonophobia, are very often reported. Headache intensity and features do not differ between primary and secondary dengue, between DF and DHF, or between patients with or without other neurologic symptoms aside from headache [6]. The headache characteristics are thus not affected by the severity of the dengue infection [6].

Dengue headache is more commonly classified as a headache attributed to systemic infection (International Headache Society Classification-II) [7]. More rarely, dengue headache can be caused by lymphocytic meningitis [8]. In such cases, it is possible to detect nuchal rigidity, Kernig’s sign, and Brudzinski’s sign [9].

Encephalitis/Meningoencephalitis

Encephalitis and meningoencephalitis have been found in 4 to 21% of dengue cases. This wide variation in the prevalence of encephalitis most likely reflects differences in the populations studied and the lack of specific criteria to define dengue encephalitis and distinguish it from other types of CNS involvement [4,10].

The most frequent finding in adult patients is altered consciousness [4] and in children is a reduced level of consciousness [11]. Other symptoms can be found, such as abnormal coordination, altered behaviour, paresis, and seizures. Nuchal rigidity may occur in meningoencephalitis cases. More severe cases can lead to lethargy and coma [4,10,11]. Brain scans by computed tomography (CT) are usually normal but may show low density signals and meningeal enhancement [12]. Brain scans by magnetic resonance imaging (MRI) may include T2-weighted contrast, with or without haemorrhage in the thalamus, cerebellum, and pons, but it is often normal [12-14]. General evaluation of cerebrospinal fluid (CSF) is usually normal but may disclose increased levels of white blood cells. Positive IgM and
IgG antibodies to the dengue virus can be found in serum and CSF, and IgG affinity tests can be useful to distinguish between primary and secondary dengue [15]. Dengue RNA has been detected in CSF samples by PCR of 50% to 83.3% of the patients with dengue encephalitis [4,16]. The viral load in CSF is low so that this can explain the low sensitivity of the CSF PCR [4].

Differential diagnoses for dengue encephalitis and meningoencephalitis include other viral-induced encephalitis, autoimmune encephalopathy, and metabolic disorders [17-21]. In cases of confirmed, acute dengue infection, it is usually extremely difficult to distinguish between dengue encephalitis, encephalopathy and acute disseminated encephalomyelitis (ADEM) [19-21], since, clinically, there is a significant amount of overlap between the symptoms of these conditions [21-31]. Diagnostic criteria for dengue encephalitis have been proposed [32,33]. According to these criteria encephalitis dengue encephalitis should be confirmed with CSF positive anti-dengue IgM and/or positive CSF for dengue RNA in order to distinguish between dengue encephalitis and dengue associated ADEM. MRI may also help in this differential diagnosis.

Some studies have demonstrated the presence of viral RNA or viral antigens in the brain or in the CSF of dengue patients, indicating that viral invasion of the CNS may occur [4,10,16]. The most frequent pathologic findings in fatal cases are cerebral oedema and haemorrhage, which are not typical findings of encephalitis due to neurotropic viruses [25,30]. These findings indicate that the pathogenic role dengue virus on CNS is still poorly known.

Post Infectious CNS manifestations

Acute Disseminated Encephalomyelitis (ADEM): Dengue virus may trigger a post-infectious autoimmune response towards myelin or other CNS antigens, possibly via molecular mimicry. Demyelination with foci of haemorrhage was found in a patient with ADEM, following dengue virus infection [34]. The neurological symptoms of dengue-related ADEM include altered consciousness, language disturbances, paresis, sensorial deficits, and altered sensorium, usually developing one or two weeks after dengue infection [34,35]. MRI findings include T1 low signal and T2 high signal lesions, with gadolinium contrast enhancement mainly located in the periventricular region, callosalseptal interface, centrum semiovale, corona radiata, and thalamus [34-36].

Neuromyelitis Ottica (NMO), Optical Neuritis (On), and Myelitis: Neumyelitis otttica (NMO), also known as Devic’s syndrome, is an autoimmune and inflammatory disorder with optic nerve and spinal cord involvement [37,38] that results in decreased visual acuity and spinal cord disorder (symmetrical weakness, reduced sensation, loss of bladder and bowel control) occurring either simultaneously or separately [37,38].

NMO, isolated ON, and isolated myelitis were described in isolated cases in association with previous dengue virus infections. Dengue-associated ON is characterised by the acute loss of vision, and papilla edema may be found by fundoscopic evaluation [39]. Dengue-associated myelitis symptoms include severe paraparesis and urinary retention [40]. Myelitis can be caused by direct viral invasion and can be limited to grey matter, preferentially to the anterior horn, as observed in poliomyelitis [41]. Myelitis with laboratory evidence of the invasion of the dengue virus into the spinal cord and the presence of the intrathecal synthesis of IgG antibodies has been reported [3]. Dengue-associated NMO causes acute vision loss, weakness of the lower limbs, hyperreflexia, and Babinski sign [42].

Peripheral neuropathies: Different forms of peripheral neuropathies have been described in association with acute dengue. The most common is Guillain-Barré syndrome (GBS). This syndrome has an incidence of 1 to 3 per 100,000 persons annually and may be triggered by several infectious agents, such as Campylobacter, Mycoplasma pneumoniae, Epstein Barr, and cytomegalovirus. It is characterised by the acute onset of weakness in the limbs and is associated with areflexia. The demyelination of peripheral nerves can be demonstrated by electrophysiological studies showing the involvement of motor and sensory nerves. Cerebrospinal fluid analyses show normal leukocyte counts with increased protein concentrations [43,44].

Several cases of GBS following acute dengue virus infections have been described, with patient ages ranging from 1.5 to 79 years old. The neurologic symptoms develop from 0 to 30 days after dengue acute febrile disease, with the average time of onset of symptoms being two weeks. The clinical course seems to be similar to other aetiologies of GBS, with most patients recovering without persisting neurologic deficits [45-52]. Cases of GBS after oligosymptomatic dengue have also been described in endemic areas [53].

Miller Fisher syndrome, with the triad of ophthalmoplegia, ataxia, and areflexia, has also been described in association with dengue virus infection [54]. Other forms of rare neuropathies, such as isolated cranial neuropathy of the abducens nerve and diaphragmatic paralysis, are also associated with dengue infection [55,56].

Another inflammatory neuropathy reported in association with dengue is neuralgic amyotrophy, also called acute brachial neuritis or Parsonage Turner syndrome. This syndrome presents as an acute onset shoulder pain, followed by the flaccid paralysis of the shoulder girdle arm musculature [57,58]. There is evidence that neuralgic amyotrophy in dengue is triggered by an immune-mediated mechanism, with antiganglioside antibodies leading to inflammatory changes. The neuropathy develops a few days after the acute infectious illness [59].

Myositis: The clinical presentation of dengue myositis includes muscle pain and, more rarely, weakness. Increased serum levels of creatinephosphokinase (CPK) are observed, and electromyography tests show typical myopathic abnormalities. Muscle biopsies were performed in some cases, showing myositis, and the pathological findings included mild to moderate perivascular infiltration and lipid accumulation. The weakness usually affects the limbs, but cases with cervical and oropharyngeal involvements have also been described [60-63]. One case of acute dengue myositis, with rhabdomyolysis and acute renal failure, has been described [64].

A possible mechanism of dengue myositis is the direct viral invasion of the muscle fibres and the production of myotoxic cytokines, particularly tumour necrosis factor (TNF) [60]. However, one case of severe, persistent, steroid-responsive dengue myositis has been described, suggesting that autoimmune mechanisms may also occur, at least in some cases [65].

Hypocalcemic paralysis: Jha and Ansari have reported pure motor quadriparesis in three patients with acute dengue infection. All of the patients recovered after potassium supplementation [66]. Gupta et al. have also described one patient with hypokalemic paralysis with acute dengue infection [67]. The patient with hypokalemic paralysis had acute tetraparesis with normal CK levels and a normal electrodiagnostic evaluation. Other causes of hypokalemic paralysis, such as thyrotoxicosis, alcohol, drugs (diuretics), gastrointestinal loss and urinary potassium wasting, should be ruled out to confirm that the hypokalemic paralysis is due to dengue [66].
Hypokalaemia in association with dengue fever has been reported in up to 28% of serologically proven cases [68]. The mechanism of the hypokalaemia could be either the redistribution of potassium in cells or transient renal tubular abnormalities, leading to increased urinary potassium wasting; however, the precise pathophysiology of hypokalaemic paralysis in dengue is not yet clear [42,66].

**Stroke:** Dengue fever is an uncommon cause of stroke. During an epidemic in Ludhiana, a total of 1148 patients with confirmed dengue were seen in a tertiary hospital, and three of them had stroke (2 had haemorrhagic stroke, and 1 had ischaemic stroke). The clinical symptoms included altered sensorium and focal neurological signs. All of the stroke victims had thrombocytopenia [69]. Another case of ischaemic stroke in dengue was reported by Liou et al. in a patient with focal neurological deficits and thrombocytopenia [70]. Brain haemorrhage is most likely related to acute-dengue-associated capillary leakage and thrombocytopenia [69]. Ischaemic stroke may be associated with meningovasculitis; however, there are not conclusive data about the mechanisms leading to brain ischemia in dengue [69].

**Clinical Management Of Dengue-Associated Neurological Disorders**

Patients with suspected dengue and neurological symptoms may present with headache (including dengue headache and dengue meningitis); altered sensorium, with or without focal neurological signs (including encephalopathy, encephalitis, ADEM, and stroke); and para- or tetraparesis (including hypokalaemic paralysis, myopathy, and GBS).

Patients with dengue headache should be treated with fluid replacement and oral analgesics. Neuroimaging and lumbar puncture are not routinely indicated in patients with dengue headache, unless there are signs of meningeal irritation or the diagnosis is not entirely clear. Some patients report headache improvement with acetaminophen or dipyrone, but nearly half of the patients with dengue headache do not improve with common analgesics [6]. Considering that dengue headache shares common features with migraines, it is important that the clinician in the emergency room evaluates the presence of systemic symptoms, such as fever and muscle pain, to distinguish these two conditions. This is especially relevant because some migraine patients take acetylsalicylic acid for headache relief, but dengue patients with an active dengue infection may not be treated with this drug due to an increased risk of haemorrhagic manifestations. Safety and efficacy studies with different classes of drugs for dengue headache relief, such as triptans, are desirable because dengue headache is severe and usually refractory to common analgesics [6].

Patients with altered sensorium, with or without focal neurological signs suggestive of dengue in the CNS, should be hospitalised and investigated. Neuroimaging, preferably MRI, and cerebrospinal fluid analysis should be ordered. Distinguishing between dengue encephalitis, encephalopathy, ADEM, and stroke may be difficult in such cases. There is no specific known treatment for dengue encephalitis [4]. The clinical approach should be performed as described elsewhere [21], with careful monitoring and the replacement of intravascular fluids and electrolyte losses through the administration of crystalloids. General management includes the monitoring and maintenance of airways and adequate oxygenation and nutrition. Seizures are common in dengue encephalitis. Usually, dengue-encephalitis-associated seizures are generalised, but cases of partial seizures have been described. Intravenous lorazepam and phenytoin are the drugs of choice. In refractory cases, intravenous midazolam can be used. There is no evidence that intravenous corticosteroids are useful in cases of dengue encephalitis [21]. In cases of NMO or ADEM, treatment with high doses of intravenous methylprednisolone, intravenous immunoglobulin or plasmapheresis is recommended [12,37-41]. Even with treatment, the clinical recovery in patients with dengue related ADEM is usually incomplete [37-41]. The treatment of stroke in patients with dengue has been based on the supportive and symptomatic treatment of neurological symptoms. Antiplatelet drugs, anticoagulants, and thrombolysis should not be considered in patients with dengue-associated coagulation disorder [69,70] due to the high risk of bleeding in dengue.

In patients with acute para- or tetraparesis, the differential diagnoses include hypokalaemic paralysis, myopathy, and GBS. An ionogram should be promptly ordered to evaluate is the presence of hypokalaemia. Patients with dengue hypokalaemic paralysis should be treated with 40 mEq potassium chloride in 500 ml of 5% dextrose [66]. There is no known treatment for dengue myositis, and most cases are related to direct viral invasion; however, steroid-responsive myopathy has previously been described, suggesting that some cases may respond to corticoids [65]. If the patient has GBS, treatment with intravenous immunoglobulin or plasmapheresis is recommended and has been associated with complete or partial clinical recovery [44-49]. If the patient has painful monoparesis, neuralgic amyotrophy should be suspected. In such cases, steroids should be used [58].

**Conclusion**

Although neurological involvement is not very frequent in patients with dengue, there are several forms of neurological involvement in patients with acute dengue virus infection. It is important that neurologists are familiar with the neurological manifestations of acute dengue, especially in endemic areas. The diagnosis of dengue should always be considered in patients with fever and acute neurological symptoms during dengue epidemics. The neurologic manifestations of dengue may resemble other acute infections and other inflammatory neurological diseases. Neuroimaging and laboratorial data may be extremely helpful in the differential diagnosis of dengue-associated neurological disorders and other acute neurological diseases. Another challenge for neurologists may be the definition of the type of neurological involvement in dengue. Some of the manifestations, such as encephalitis, encephalopathy, ADEM, and stroke, may share clinical symptoms. For the precise distinction between these conditions, neuroimaging and laboratory studies are also necessary. Therefore, the availability of radiological methods, especially MRI and CSF analysis, including molecular and immunological evaluation, increases the diagnostic precision. Beyond the definition of the type of neurological involvement in dengue, diagnostic precision may have therapeutic implications. For instance, ADEM, but not encephalitis, requires a specific treatment with high doses of corticoids. Dengue often occurs in developing areas where hospitals do not always have these technologies available. It is possible that dengue-associated neurological disorders, as well as their potentially confounding diseases, have been under- and misdiagnosed in such areas. Therefore, the precise burden of dengue-associated neurological disorders is still unknown. Future studies with the systematic use of such diagnostic technology in suspected cases may provide a better understanding of the prevalence and prognosis of dengue-associated neurological disorders, allowing a better understanding of the burden of neurological involvement in the context of dengue virus infection.
References


