Frassetto FP, et al. J Phys Med Rehabil Disabil 2021, 7: 066
DOI: 10.24966/PMRD-8670/100066

HSOA Journal of
Physical Medicine, Rehabilitation and Disabilities

Research Article

Neurological and Neuropathological Findings in Dengue: A Review

Fernando Pereira Frassetto*

Faculdade de Medicina da Universidade de São Paulo, Brazil

Abstract

Dengue is an infectious disease endemic in large regions of the world, caused by the dengue virus, subtypes 1 to 4, transmitted by mosquitoes of the *Aedes* genus. It is a disease that affects multiple organs and systems, with broad clinical spectrum, ranging from mild symptoms to fatal hemorrhagic syndromes. When there are associated neurological alterations, such as encephalopathy, encephalitis, meningitis, Guillain-Barre syndrome, among others, it is called Expanded Dengue Syndrome (EDS).

Methods

Review of the literature regarding neurological manifestations and neuropathological changes associated with dengue.

Results

Neuropathological descriptions are relatively scarce in the literature, and are more commonly related as disturbances of vascular function and integrity, such as edema and hemorrhage. A few studies describe the presence of inflammatory processes in the parenchyma (encephalitis, myelitis) and in muscle biopsies. Ischemic alterations (microinfarcts), perivenous demyelination, neuronal eosinophilic alterations associated with acute injury, gliosis, and microglial reactivity, are also documented.

Conclusion

The presence of neuropathological alterations is well established in the literature, but more of these descriptions are needed for a better understanding of the pathogenesis of the important neurological alterations seen in expanded dengue syndrome.

Keywords: Arbovirosis; Dengue; Encephalitis; Hemorrhage; Neuropathology

***Corresponding author:** Fernando Pereira Frassetto. Faculdade de Medicina da Universidade de São Paulo, São Paulo Brazil, Tel: +55 11981212830; E-mail: fernando.frassetto@hc.fm.usp.br

Citation: Frassetto FP (2021) Neurological and Neuropathological Findings in Dengue: A Review. J Phys Med Rehabil Disabil 7: 66.

Received: August 10, 2021; **Accepted:** August 23, 2021; **Published:** August 30, 2021

Introduction

Dengue is an arbovirosis caused by the Dengue Virus (DENV), an RNA-virus of the flaviviridae family, composed of four serotypes (called DENV-1 to DENV-4). It is transmitted to humans by mosquitoes, most commonly of the *Aedes* genus [1]. It is an endemic disease in several parts of the world, especially in tropical and subtropical regions, where epidemics occur frequently [2]. The incidence of dengue has grown around the world in recent decades. The number of dengue cases reported to the World Health Organization (WHO) increased over eight fold over the last two decades, from 505,430 cases in 2000, to over 2.4 million in 2010, and 5.2 million in 2019. Reported deaths between the year 2000 and 2015 increased from 960 to 4032. In 2021, still amidst the Coronavirus Disease (COVID-19) pandemic, endemic and mosquito-borne infections such as dengue are at potential risk of underreporting, underdiagnoses and reduced prevention measures, being a neglected disease that mainly affects underdeveloped countries. The combined impact of COVID-19 and dengue epidemics can potentially result in devastating consequences for the populations at risk [3].

According to WHO, in the revised and expanded edition of its comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever, published in 2011, defines the different types of clinical presentation? The more nonspecific form, called undifferentiated fever, is common in infants, children and adults who have been infected with dengue virus, especially for the first time. The Dengue Fever (DF) is generally an acute febrile illness, and sometimes biphasic fever, which is generally self-limiting, and most common in older children, adolescents and adults. The more severe form is called severe dengue fever or Dengue Hemorrhagic Fever (DHF), more common in children less than 15 years of age in hyperendemic areas, and associated with repeated dengue infections. DHF can develop into a Dengue Shock Syndrome (DSS), which may be preceded by warning signs such as persistent vomiting, lethargy or restlessness, or irritability and oliguria [4].

The severity of clinical repercussions depends on multiple factors associated with the complex interaction between the host, especially its immune system, and the infectious agent [5-9]. Unusual or atypical manifestations have been designated Expanded Dengue Syndrome (EDS). These manifestations include the neurological impairment, such as seizures, lowered level of consciousness and motor disturbances (spasticity, transient paresis), and associated with multiple tissue changes (hemorrhages, edema, and inflammatory processes, among others) [4,10]. Unfortunately, in most of the non-fatal cases in well-known series, an autopsy was not performed, not allowing for an adequate histopathological analysis [4].

In this paper, aspects of dengue with neurological involvement are reviewed, as well as neuropathological findings described both in animal models and in human case reports and series, especially autopsies. Some aspects of the pathogenesis of these alterations are also discussed.

Methods

The literature was searched through Pubmed, Cochrane Library and Google Scholar for case reports, series of cases, research articles and reviews, addressing neurological manifestations and neuropathological findings in dengue. Papers describing the pathogenesis of neurological alterations, their epidemiology, and animal models used to demonstrate such alterations were also searched.

Results

Neurological manifestations

Neurological manifestations, in its clinical aspects, have been described in dengue since the 1960s [11-13] and, in some cases, the neurological presentation may be the first one related to the infection. Historically, such manifestations were considered secondary mainly to systemic alterations, especially vascular ones, and not to the presence of the virus, considered non-neurotropic [14]. However, in recent decades, the neurotropism of DENV has been solidly demonstrated, with antigens and viral RNA being isolated both in tissues of the Central Nervous System (CNS) and Peripheral Nervous System (PNS), as well as in the Cerebrospinal Fluid (CSF) [15-24]. Serotypes 2 and 3 have been described as having the greatest potential to induce neurological disturbances, acting as neurovirulent elements similar to other flaviviruses [15,19,25-29]. Some clinical and laboratory parameters, like higher mean body temperature, low platelet count, elevated hematocrit, and liver dysfunction, have been described as risk factors for neurological dysfunction [30].

Neurological alterations associated with dengue are classified in different ways, with different criteria. Some authors prefer to use the mechanisms of pathogenesis as classifiers: Metabolic disturbances, resulting predominantly in encephalopathy; viral invasion, mainly associated with encephalitis, meningitis, myelitis and myositis; and exacerbated autoimmunity, including neuromyelitis optica, optic neuritis, Acute Disseminated Encephalomyelitis (ADEM) and Guillain-Barre syndrome [7,31,32]. Encephalopathy is strongly associated with DSS, due to the hydroelectrolytic, inflammatory and vascular alterations inherent to the shock condition, as well as commonly associated hepatic and renal injuries, and the possible presence of the virus in the tissue [21,33,34].

A characteristic finding of some cases is the Cerebellar syndrome mentioned by Weeratunga and colleagues, which described bilateral vertical and horizontal nystagmus, dysarthria, bilateral limb, and gait ataxia. A low-grade inflammatory process was the proposed mechanism [35]. Solbrig and Perng, when proposing their classification, include cerebellitis in a broad category composed of inflammatory changes (encephalitis, meningitis, meningoencephalitis, myelitis, acute disseminated encephalomyelitis, and retinochoroiditis) and vascular disturbances (subdural hematoma, ischemic or hemorrhagic stroke, intracranial hemorrhage, cerebral vasculitis, retinal vasculopathy). Other categories proposed in this classification include encephalopathy, characterized by depressed sensitivity, cognitive disorders, convulsions, mood, personality and behavior disorders; peripheral nervous system syndromes, including Guillain-Barré, acute motor sensory axonal neuropathy, multiplex mononeuritis, brachial plexitis, hypokalemic quadriparesis or plegia, diaphragmatic paralysis, and myositis; and convalescent or post-dengue immune-mediated syndromes (ADEM, transverse myelitis, neuromyelitis optica, cranial neuropathies, arteritis, Miller-Fisher syndrome and arteritis) [21]. Some excellent reviews were published on the neurological disorders associated with dengue in recent years [36,37].

The pathogenesis of neurological disorders is not fully understood. Various mechanisms that have been suggested include enhancing antibodies in secondary dengue, memory T-cell-mediated pathogenesis, immune complex disease, complement and its products, anti-NS1 antibodies that cross-react with vascular endothelium, cytokine "storm" and other soluble mediators, together with possible selection of virulent virus strains and host genetic polymorphism [38]. The penetration of DENV into the CNS may occur through areas of hemorrhage, regions of plasma transudation, and/or damage to the blood-brain barrier by action mainly of inflammatory cells, but also of the virus itself [38,39]. DENV preferentially infects monocyte lineage cells [40,41]. Endothelial cells, neurons, glial cells and microglia are proven to be suitable receptor cells for the virus [39,42,43].

Neuropathological findings in humans and animal models

Morphological, both macroscopic and microscopic, descriptions associated with neurological signs and symptoms in dengue are limited in the literature, as most cases are non-fatal [44], biopsies are rarely needed in these individuals and, of those with a fatal evolution, only a variable percentage undergoes autopsy, the main method of obtaining tissue for analysis. Various techniques often performed in vivo for evaluating neuropathological alterations, such as Magnetic Resonance Imaging (MRI) and CSF laboratory analysis, allow us to obtain important information related to such alterations, without, however, replacing the histopathological evaluation.

Animal models are useful to demonstrate neuropathological changes in this context of limited amounts of material available. An and colleagues inoculated DENV-2 into the brain tissue of immunodeficient mice, and observed dissemination of the virions, to both brain and spinal cord neurons, and to myelinated and unmyelinated nerve fibers, suggesting spread through the CSF. On histopathological evaluation, they observed several pathological changes in the spinal cord, including edema and congestion, neuronal changes including decreased Nissl substance, vacuolization and neuronophagia. Astrocyte swelling was occasionally seen. With the virus replication, loss of the neurons was observed in the spinal cord anterior horn [45]. Bordignon and colleagues performed intracerebral inoculation of neuroadapted DENV1 strains in mice, and described intense chronic lymphohistiocytic leptomeningitis and moderate encephalitis, with neuronal necrosis (red neurons), satellitosis of lymphocytes and microglia around dying neurons, and the presence of microglial nodules and perivascular lymphocytes. They compared the findings with strains considered to be non-neuroadapted, which showed much more mild inflammatory changes, predominantly in leptomeninges [46].

Amaral and colleagues inoculated DENV-3 intracranially in mice, and observed mild gliosis and multifocal areas of perivascular hemorrhages in brainstem, diffuse meningeal infiltration of neutrophils, mononuclear cells infiltration with associated vasculitis in brain and cerebellum, numerous rod-shaped microglial cells and intense neuronal destruction of the pyramidal layer (CA3 and CA4) of the hippocampus. They performed semi-quantitative analysis (0 to 4-point scale), and assessed the density of necrotic and apoptotic cells, thereby demonstrating progressive pathological changes in the meninges, cerebral cortex, cerebellum, hippocampus and brainstem [47].

Amorim and colleagues inoculated DENV2 in BALB/c mice by the intracerebral route, and several animals presented clinical manifestations related to neurological disorders and succumbed to the disease. They demonstrated several changes in brain tissue: Hemorrhages, microglial hyperplasia and hypertrophy, perivascular,

meningeal and parenchymal inflammatory infiltrate (predominantly lymphocytic), and focal areas of reactive gliosis.They also performed a semiquantitative score (0 to 4-point scale) to measure histological changes, which demonstrated that the inflammatory infiltrates, as those found in the pia mater, showed a sustained increase until the end of the experiment, the same pattern being observed in relation to the perivascular infiltrates.In the cerebellar tissue, changes were similar, but milder than those observed in the brain, and morphological changes (retraction) in Purkinje neurons were observed. The authors demonstrated viral tropism and replication in resident cells of the brain and cerebellum, such as neurons, astrocytes, microglia and oligodendrocytes, and cited viral neuroadaptation as important in keeping the virus in the nervous tissue. The associated immune response was considered the main responsible for the observed histopathological alterations [48].

In reports and case series in humans, the main morphological changes in the CNS are associated with vascular alterations, especially plasma leakage and loss of wall integrity. Cerebral edema is a frequent alteration, both on MRI and gross evaluation, and it is mainly associated with the clinical aspects of encephalopathy [49]. Edema is a process that can be routinely grossly evaluated, and Burke, in his pioneering work, described changes like an increase in brain weight, as well as meningeal congestion and edema, in all the 12 cases evaluated [50]. Other authors described the changes associated with edema as an increase in brain mass and volume, obliteration of the sulci and flattening of the gyri, and meningeal congestion, or simply as brain edema [51-57]. Massive cerebral edema with consequent hemorrhage and bilateral tonsillar herniation leading to death was also described [57]. By microscopic evaluation, Bhamarapravati and colleagues, in another pioneering work, described cerebral cortex, basal ganglia, pons, midbrain or medulla samples from a collection of 42 brains, and found microscopic edema-related changes (prominence of Virchow-Robin spaces, arachnoid layer edema) in “most cases” [58]. Other relevant papers describe parenchymal and/or perineuronal vacuolation, meningeal edema, and associated vascular congestion [50-57].

Hemorrhagic events were also frequently described, both in fatal and non-fatal cases, mainly in MRI. These events take the many forms, such petechial, focal, multifocal, or even extensive hemorrhages, affecting different areas of the cerebral lobes, basal ganglia (sometimes with ventricular extension), cerebellum and pons, as well as meninges, in subarachnoid and subdural spaces, and epidural compartment [28,50-52,54,56,58-70]. Coagulation disorders, present in hemorrhagic forms of dengue, as well as the previously mentioned immune-mediated damage to endothelial cells and direct viral activity and injury to endothelial cells, were associated with bleeding events [27,39,40,58]. At the microscopic level, some authors showed diffuse thickening of white matter capillaries, sometimes with degeneration of elements of the vascular wall, and consequent weakening and ruptures [52,56]. Miagostovich and colleaguesdemonstrated, with immunohistochemical methods, virus-positive cells, mostly located within Virchow Robin space of medium size and small veins, infiltrating the white and grey matter, and often situated close to neurons displaying apparent cytopathic features. Furthermore, immunostaining for CD68 antigens demonstrated that most CD68-positive macrophages and dengue antigen-positive cells share similar morphology and localization, and suggested a unique identity for at least part of the cells, possibly responsible for the penetration of the virus into the CNS through the vessels [16]. Ischemic alterations are reported in the literature, but with little anatomopathological substrate, as the cases are generally non-fatal, MRI being the main evaluation method [68,71,72]. Jois and colleagues described multiple microinfarcts throughout the midbrain, pons, medulla, cerebellum, cerebral cortex, and dura mater [57].

Regarding inflammatory processes, predominantly lymphomononuclear infiltrate affecting the perivascular compartment, without obvious encephalitic aspects, was described by some authors [52,56,63]. An encephalitic process is described by Jois and colleagues in three fatal cases, with a predominantly lymphomononuclear multifocal infiltrate, and scattered foci of neutrophils. The authors graded both inflammation and edema in semi quantitative scale (0 to 3-point), and found a significant association between the inflammation and edema in the medulla, pons, and midbrain, as wells as significant association between the frontal and temporal lobes, and the occipital and parietal lobes. They also suggested that inflammation in cases of dengue encephalitis is relatively more intense in the forebrain structures, and that the edema in the medulla, pons, and midbrain was probably a terminal event leading to death [56].

Pathological changes in brain parenchyma cells are also documented in the literature, like neuronal eosinophilic alterations associated with acute injury (red neuron), gliosis and microglial reactivity [56,58,73]. Salomão and colleagues showed intense neuronal degeneration, with some nuclei displaced to the periphery of the neuron, in the cortical area with no relevant alterations on the neuropil. The same authors proposed a quantitative analysis of glial cell numbers in cortex and white matter areas, compared with controls, and found an increment in both compartments in cases, compared to controls, demonstrating significant glial reactivity. In their important work, they also conducted a morphological analysis using immunohistochemical markers, showing hyperplasia of microglial cells. The astrocyte population also presented altered morphology - thicker and less numerous extensions either in the cortical area or in the white matter around blood vessels, compared to controls [56].

Descriptions of the neuropathological substrate of other neurological changes, especially related to inflammatory response, are scarce in the literature, although they are well documented by complementary techniques. Meningitis is a rare complication, usually determined by clinical signs and laboratory alterations (like lymphocytic pleocytosis) in the CSF, and not by tissue evaluation [74-77]. Transverse myelitis, or longitudinally extensive transverse myelitis, is alterations also commonly evaluated by CSF analysis, as well as MRI [67,70,78-86]. A specific form of involvement of the CNS is ADEM, and its assessment is predominantly through MRI [80,87-92]. Sometimes there is an association with hemorrhage [93]. Few studies describe the ADEM alterations histologically as perivenous demyelination in the brain parenchyma [51,63].

Clinical features of myositis associated with dengue are very frequent, but there are few histopathological descriptions. Malheiros and colleagues studied fifteen muscular biopsies, and found perivascular mononuclear infiltrates (but no myositis), lipid accumulation, mild mitochondrial proliferation, few central nuclei, and rare foci of myonecrosis, but direct invasion of skeletal muscle by the dengue virus has not been demonstrated [94]. Kalita and colleagues described a muscular biopsy containing necrotic fibers with evidence of regeneration, interstitial inflammatory reaction containing clusters of mononuclear and polymorphonuclear cells, and myophagocytosis, findings suggestive of myositis [95]. Variation in fiber size, hyalinization and myophagocytois were described by Misra and colleagues in one muscular biopsy [96].

Discussion

Being a disease widely spread across the globe, affecting a large number of people, the neurological alterations associated with dengue, clinically grouped in the so-called expanded dengue syndrome, is well known, and cause for concern, to the medical community. Complementary methods such as MRI and CSF laboratory analysis are very useful in the evaluation of non-fatal cases. However, despite a substantial number of deaths, descriptions of neuropathological alterations are scarce in the literature. Some animal models make it possible to document several neuropathological findings. As previously described, alterations are generally present in greater intensity and more diffusely than in humans. The mode of infection (intracerebral injection inoculation) by viral strains contributes to these findings, allowing for a higher viral load.

As we have seen, viral neurotropism is already well documented in the literature. The presence of the virus in the nervous system, associated with an exacerbated immune response, and vascular and metabolic disorders, results in several alterations, such as encephalopathy, encephalitis, meningitis, vasculitis, Guillain-Barre syndrome, myositis, various types of hemorrhagic phenomena, among others. These phenomena are more often evaluated by complementary methods, such as MRI and CSF laboratory analysis, in non-fatal cases.

In case reports and series, most commonly autopsies, the most frequent neuropathological findings are those related to disturbances of vascular function and integrity, such as edema and hemorrhage. There are descriptions of hemorrhagic phenomena of widely variable aspects and extension, affecting any compartment - parenchyma (brain, cerebellum, brainstem, and spinal cord), ventricular system, subarachnoid, subdural and epidural spaces. Ischemic phenomena, less frequent than hemorrhagic ones, are also described.

A few studies showed the presence of an inflammatory infiltrate, usually lymphomononuclear, in the parenchyma (encephalitis, myelitis) and around vessels (perivascular, sometimes vasculitis). In particular, the work of Jois and colleagues establishes degrees of parenchymal inflammation, and correlates them with changes associated with edema [57]. Pathological responses in brain parenchyma cells like neuronal eosinophilic alterations associated with acute injury ("red neuron"), gliosis, and microglial reactivity, are also documented in some papers. Other neuropathological aspects that are described in the literature are perivenous demyelination in the brain parenchyma (in the context of ADEM) and myositis in a limited number of muscle biopsies.

It is interesting to note that some authors introduce semiquantitative rating scales for some histological parameters (such as edema, inflammation), both in animal and human models [47,48,57]. Others performed quantitative analysis of neuroglial cell numbers compared to controls using immunohistochemical methods [56]. These types of approaches allow for a more objective, measurable assessment of morphologically observed phenomena, and could be further disseminated in future work.

From the above, it is clear that the presence of neuropathological alterations is well established in the literature, but more of these descriptions are needed for a better understanding of the pathogenesis of the important neurological alterations seen in expanded dengue syndrome. Animal models can also help achieve these goals. A more complete understanding of the effects of dengue on the nervous system, which includes an adequate and extensive tissue evaluation, in particular through autopsies, can result in more effective treatments and care protocols in an often neglected disease.

Author's Disclosures

The author has no ethical or financial disclosures.

Acknowledgment

Sergio Rosemberg, MD, PhD, Faculdade de Medicina da Universidade de São Paulo, Brazil; Aline A. Giongo, MD, Universidade Nacional de Brasília, Brazil.

References

1. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, et al. (2010) Dengue: A continuing global threat. Nat Rev Microbiol 8: 7-16.
2. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, et al. (2012) Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis 6: 1760.
3. World Health Organization (2021) Dengue and severe dengue. World Health Organization, Geneva, Switzerland.
4. World Health Organization (2011) Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. Revised and expanded edition. World Health Organization, Geneva, Switzerland.
5. Monath TP (1994) Yellow fever and dengue - the interactions of virus, vector and host in the re-emergence of epidemic disease. Seminars in virology 5: 133-145.
6. Halstead SB (1998) Emergence mechanisms in yellow fever and dengue. Emerging Infections. 2: 65-79.
7. Murthy JM (2010) Neurological complications of dengue infection. Neurol India 58: 581-584.
8. Huy NT, Van Giang T, Thuy DHD, Kikuchi M, Hien TT, et al. (2013) Factors associated with dengue shock syndrome: A systematic review and meta-analysis. PLoS Negl Trop Dis 7: 2412.
9. Carabali M, Hernandez LM, Arauz MJ, Villar LA, Ridde V (2015) Why are people with dengue dying? A scoping review of determinants for dengue mortality. BMC Infect Dis 15: 1-14
10. Kadam DB, Salvi S, Chandanwale A (2016) Expanded Dengue. J Assoc Physicians India 64: 59-63.
11. Nelson ER, Chulajata R (1965) Danger signs in Thai hemorrhagic fever (dengue). J Pediatr 67: 463-470.
12. Sanguansermsri T, Poneprasert B, Phornphutkul B (1976) Acute encephalopathy associated with dengue infection. Southeast Asian J Trop Med Public Health 10.
13. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, et al. (2000) Neurological manifestations of dengue infection. Lancet 355: 1053-1059.
14. Nathanson N, Cole GA (1970) Immunosuppression and experimental virus infection of the nervous system. Adv Virus Res 16: 397-428.
15. Lum LC, Lam SK, Choy YS, George R, Harun F (1996) Dengue encephalitis: A true entity? Am Trop Med Hyg 54: 256-259.
16. Miagostovich MP, Ramos RG, Nicol AF, Nogueira RM, Cuzzi-Maya T, et al. (1997) Retrospective study on dengue fatal cases. Clin Neuropathol 16: 204-208.
17. Ramos C, Sánchez G, Pando RH, Baquera J, Hernández D, et al. (1998) Dengue virus in the brain of a fatal case of hemorrhagic dengue fever. J Neurovirol 4: 465-468.
18. Angibaud G, Luaute J, Laille M, Gaultier C (2001) Brain involvement in Dengue fever. J Clin Neurosci 8: 63-65.

19. Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, et al. (2001) Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg 65: 848-851.

20. Araújo FM, Brilhante RS, Cavalcanti LP, Rocha MF, Cordeiro RA, et al. (2011) Detection of the dengue nonstructural 1 antigen in cerebral spinal fluid samples using a commercially available enzyme-linked immunosorbent assay. J Virol Methods 177: 128-131.

21. Solbrig MV, Perng GC (2015) Current neurological observations and complications of dengue virus infection. Curr Neurol Neurosci Rep 15: 29.

22. Kyaw AK, Ngwe Tun MM, Nabeshima T, Buerano CC, Ando T, et al. (2019) Japanese Encephalitis- and Dengue-Associated Acute Encephalitis Syndrome Cases in Myanmar. Am J Trop Med Hyg 100: 643-646.

23. Mello CDS, Cabral-Castro MJ, Silva de Faria LC, Peralta JM, Puccioni-Sohler M (2020) Dengue and chikungunya infection in neurologic disorders from endemic areas in Brazil. Neurol Clin Pract 10: 497-502.

24. Cunha MDP, Duarte-Neto AN, Pour SZ, Hajjar LA, Frassetto FP, et al. (2021) Systemic dengue infection associated with a new dengue virus type 2 introduction in Brazil - a case report. BMC Infect Dis 21: 311.

25. Sistayanarain A, Maneekarn N, Polprasert B, Sirisanthana V, Makino Y, et al. (1996) Primary sequence of the envelope glycoprotein of a dengue type 2 virus isolated from patient with dengue hemorrhagic fever and encephalopathy. Southeast Asian J Trop Med Public Health 27: 221-227.

26. Miagostovich MP, dos Santos FB, Fumian TM, Guimarães FR, da Costa EV, et al. (2006) Complete genetic characterization of a Brazilian dengue virus type 3 strain isolated from a fatal outcome. Mem Inst Oswaldo Cruz 101: 307-313.

27. Seet RC, Lim EC (2007) Dysarthria-clumsy hand syndrome associated with dengue type-2 infection. J Neurol 254: 1129-1130.

28. Vargas-Sánchez A, Chiquete E, Gutiérrez-Plascencia P, Castaneda-Moreno V, Alfaro-Castellanos D, et al. (2014) Cerebellar hemorrhage in a patient during the convalescent phase of dengue fever. J Stroke 16: 202-204.

29. Ngwe Tun MM, Muthugala R, Nabeshima T, Soe AM, Dumre SP, et al. (2020) Complete genome analysis and characterization of neurotropic dengue virus 2 cosmopolitan genotype isolated from the cerebrospinal fluid of encephalitis patients. PLoS One 15: 0234508.

30. Sahu R, Verma R, Jain A, Garg RK, Singh MK, et al. (2014) Neurologic complications in dengue virus infection: a prospective cohort study. Neurology 83: 1601-1609.

31. Puccioni-Sohler M, Orsini M, Soares CN (2012) Dengue: A new challenge for neurology. Neurol Int 4: 15.

32. Verma R, Sahu R, Holla V (2014) Neurological manifestations of dengue infection: A review. J Neurol Sci 346: 26-34.

33. Matlani M, Chakravarti A, Rawal A, Kashyap B, Gurtoo A (2009) Dengue encephalitis: An entity now common in dengue-prone regions. Tropical Doctor 39: 115-116.

34. Sumarmo WH, Jahja E, Gubler DJ, Sutomenggolo TS, Saroso JS (1978) Encephalopathy associated with dengue infection. Lancet 1: 449-50.

35. Weeratunga PN, Caldera HP, Gooneratne IK, Gamage R, Perera WS, Ranasinghe GV, et al. (2014) Spontaneously resolving cerebellar syndrome as a sequelae of dengue viral infection: A case series from Sri Lanka. Pract Neurol 14: 176-178.

36. Carod-Artal FJ, Wichmann O, Farrar J, Gascón J (2013) Neurological complications of dengue virus infection. Lancet Neurol 12: 906-919.

37. Li GH, Ning ZJ, Liu YM, Li XH (2017) Neurological Manifestations of Dengue Infection. Front Cell Infect Microbiol 7: 449.

38. Basu A, Chaturvedi UC (2008) Vascular endothelium: the battlefield of dengue viruses. FEMS Immunol Med Microbiol 53: 287-299.

39. Bastidas-Legarda LY, Beltrán EO, Camacho-Ortega SJ, Castellanos JE (2019) Dengue virus infection of blood-brain barrier Cells: Consequences of severe disease. Front Microbiol 10: 1435.

40. Scott RM, Nisalak A, Cheamudon U (1980) Isolation of dengue viruses from peripheral blood leukocytes of patients with hemorrhagic fever. J Infect Dis 141: 1-6.

41. Salazar MI, Pérez-García M, Terreros-Tinoco M, Castro-Mussot ME, Diegopérez-Ramírez J, et al. (2013) Dengue virus type 2: Protein binding and active replication in human central nervous system cells. Scientific World Journal 2013: 904067.

42. Ramos C, Sánchez G, Pando RH, Baquera J, Hernández D, et al. (1998) Dengue virus in the brain of a fatal case of hemorrhagic dengue fever. J Neurovirol 4: 465-468.

43. Lin C-F, Chiu S-C, Hsiao Y-L, Wan S-W, Lei H-Y, et al. (2005) Expression of cytokine, chemokine, and adhesion molecules during endothelial cell activation induced by antibodies against dengue virus nonstructural protein 1. J Immunol 174: 395-403.

44. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, et al. (2013) The global distribution and burden of dengue. Nature 496: 504-507.

45. An J, Zhou D-S, Kawasaki K, Yasui K (2003) The pathogenesis of spinal cord involvement in dengue virus infection. Virchows Arch 442: 472-481.

46. Bordignon J, Strottmann DM, Mosimann AL, Probst CM, Stella V, et al. (2007) Dengue neurovirulence in mice: Identification of molecular signatures in the E and NS3 helicase domains. J Med Virol 79: 1506-15017.

47. Amaral DCG, Rachid MA, Vilela MC, Campos RDL, Ferreira GP, et al. (2011) Intracerebral infection with dengue-3 virus induces meningoencephalitis and behavioral changes that precede lethality in mice. J Neuroinflammation 8: 23.

48. Amorim JFS, Azevedo AS, Costa SM, Trindade GF, Basilio-de-Oliveira CA, et al. (2019) Dengue infection in mice inoculated by the intracerebral route: Neuropathological effects and identification of target cells for virus replication. Sci Rep 9: 17926.

49. Hendarto SK, Hadinegoro SR (1992) Dengue encephalopathy. Acta Paediatr Jpn 34: 350-357.

50. Burke T (1968) Dengue haemorrhagic fever: A pathophysiological study. Trans R Soc Trop Med Hyg 62: 682-693.

51. Chimelli L, Hahn MD, Netto MB, Dias M, Gray F (1990) Dengue: Neuropathological findings in 5 fatal cases from Brazil. Clin Neuropathol 9: 157-162.

52. Janssen HL, Bienfait HP, Jansen CL, van Duinen SG, Vriesendorp R, et al. (1998) Fatal cerebral oedema associated with primary dengue infection. J Infect 36: 344-346.

53. Nogueira RMR, Filippis AMB, Coelho JMO, Sequeira PC, Schatzmayr HG, et al. (2002) Dengue virus infection of the central nervous system (CNS): A case report from Brazil. Southeast Asian J Trop Med Public Health 33: 68-71.

54. Rathi KR, Arora MM, Sahai K, Tripathi S, Singh SP, et al. (2013) Autopsy findings in fatal dengue haemorrhagic fever - 06 Cases. Med J Armed Forces India 69: 254-259.

55. Póvoa TF, Alves AMB, Oliveira CAB, Nuovo GJ, Chagas VLA, et al. (2014) The pathology of severe dengue in multiple organs of human fatal cases: Histopathology, ultrastructure and virus replication. PLoS One 9: 83386.

56. Salomão N, Rabelo K, Basílio-de-Oliveira C, Basílio-de-Oliveira R, Geraldo L, et al. (2020) Fatal Dengue Cases Reveal Brain Injury and Viral Replication in Brain-Resident Cells Associated with the Local Production of Pro-Inflammatory Mediators. Viruses 12: 603.

57. Jois D, Moorchung N, Gupta S, Mutreja D, Patil S (2018) Autopsy in dengue encephalitis: An analysis of three cases. Neurol India 66: 1721-1725.

58. Bhamarapravathi N, Tuchinda P, Boonyapaknavik V (1967) Pathology of Thailand hemorrhagic fever: A study of 100 autopsy cases. Ann Trop Med Parasitol 61: 500-510.

59. Thakare J, Walhekar B, Banerjee K (1996) Hemorrhagic manifestations and encephalopathy in cases of dengue in India. Southeast Asian J Trop Med Public Health 27: 471-475.

60. de Souza LJ, Martins ALO, Paravidini PCL, Nogueira RMR, Neto CG, et al. (2005) Hemorrhagic encephalopathy in dengue shock syndrome: A case report. Braz J Infect Dis 9: 257-261.

61. Kumar J, Kumar A, Gupta S, Jain D (2007) Dengue haemorrhagic fever: An unusual cause of intracranial haemorrhage. J Neurol Neurosurg Psychiatry 78: 253.

62. Kumar R, Prakash O, Sharma BS (2009) Intracranial hemorrhage in dengue fever: Management and outcome: A series of 5 cases and review of literature. Surg Neurol 72: 429-433.

63. Sundaram C, Uppin SG, Dakshinamurthy KV, Borgahain R (2010) Acute disseminated encephalomyelitis following dengue hemorrhagic fever. Neurol India 58: 599-601.

64. Khanna A, Atam V, Gupta A (2011) A case of dengue encephalitis with intracerebral hemorrhage. J Glob Infect Dis 3: 206-207.

65. Assir MZK, Jawa A, Ahmed HI (2012) Expanded dengue syndrome: Subacute thyroiditis and intracerebral hemorrhage. BMC Infect Dis12: 240.

66. Bharti P, Bala K (2015) Subdural effusion in dengue patient as a late neurological complication: A Rare Case Report. J Clin Diagn Res 9: OD01-OD02.

67. Fong CY, Hlaing CS, Tay CG, Kadir KAA, Goh KJ, et al. (2016) Longitudinal extensive transverse myelitis with cervical epidural haematoma following dengue virus infection. Eur J Paediatr Neurol 20: 449-453.

68. Estofolete CF, Milhim BHGA, Zini N, Scamardi SN, Selvante JD, et al. (2020) Flavivirus infection associated with cerebrovascular events. Viruses 12: 671.

69. Jagadishkumar K, Ramesh S, Manapati R, Kumar HCK (2020) Acute dengue hemorrhagic Encephalitis in a Child: A case report. J Pediatr Neurosci 15: 416-420.

70. Vyas S, Ray N, Maralakunte M, Kumar A, Singh P, et al. (2020) Pattern recognition approach to brain MRI findings in patients with dengue fever with neurological complications. Neurol India 68: 1038-1047.

71. Mathew S, Pandian JD (2010) Stroke in patients with dengue. J Stroke Cerebrovasc Dis 19: 253-256.

72. Verma R, Sahu R, Singh AS, Atam V (2013) Dengue infection presenting as ischemic stroke: An uncommon neurological manifestation. Neurol India 61: 317-318.

73. Lee KM, Chiu KB, Sansing HA, Didier PJ, Lackner AA, et al. (2016) The flavivirus dengue induces hypertrophy of white matter astrocytes. J Neurovirol 22: 831-839.

74. Soares CN, Faria LC, Peralta JM, de Freitas MR, Puccioni-Sohler M (2006) Dengue infection: Neurological manifestations and Cerebrospinal Fluid (CSF) analysis. J Neurol Sci 249: 19-24.

75. Soares CN, Cabral-Castro MJ, Peralta JM, Freitas MR, Puccioni-Sohler M (2010) Meningitis determined by oligosymptomatic dengue virus type 3 infection: Report of a case. Int J Infect Dis 14: e150-e152.

76. Soares CN, Cabral-Castro MJ, Peralta JM, de Freitas MR, Zalis M, et al. (2011) Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. J Neurol Sci 303: 75-79.

77. Mamdouh KH, Mroog KM, Hani NH, Nabil EM (2013) Atypical dengue meningitis in makkah, saudi arabia with slow resolving, prominent migraine like headache, phobia, and arrhythmia. J Glob Infect Dis 5: 183-186.

78. Sindic CJ, Van Antwerpen MP, Goffette S (2001) The intrathecal humoral immune response: Laboratory analysis and clinical relevance. Clin Chem Lab Med 39: 333-40.

79. Leão RN, Oikawa T, Rosa ES, Yamaki JT, Rodrigues SG, et al. (2002) Isolation of dengue 2 virus from a patient with central nervous system involvement (transverse myelitis). Rev Soc Bras Med Trop 35: 401-404.

80. Kunishige M, Mitsui T, Tan BH, Leong HN, Takasaki T, et al. (2004) Preferential gray matter involvement in dengue myelitis. Neurology 63: 1980-1981.

81. Wasay M, Channa R, Jumani M, Shabbir G, Azeemuddin M, et al. (2008) Encephalitis and myelitis associated with dengue viral infection clinical and neuroimaging features. Clin Neurol Neurosurg 110: 635-40.

82. Chanthamat N, Sathirapanya P (2010) A cute transverse myelitis associated with dengue viral infection. J Spinal Cord Med 33: 425-427.

83. Larik A, Chiong Y, Lee LC, Ng YS (2012) Longitudinally extensive transverse myelitis associated with dengue fever. BMJ Case Rep 2012: Bcr1220115378.

84. De Sousa AM, Alvarenga MP, Alvarenga RM (2014) A cluster of transverse myelitis following dengue virus infection in the brazilian Amazon region. Trop Med Health 42: 115-1120.

85. Mo Z, Dong Y, Chen X, Yao H, Zhang B (2016) A cute transverse myelitis and subacute thyroiditis associated with dengue viral infection: A case report and literature review. Exp Ther Med 12: 2331-2335.

86. Mota MT, Estofolete CF, Zini N, Terzian AC, Gongora DV, et al. (2017) Transverse Myelitis as an Uunusual complication of dengue fever. Am J Trop Med Hyg 96: 380-381.

87. Yamamoto Y, Takasaki T, Yamada K, Kimura M, Washizaki K, et al. (2002) Acute disseminated encephalomyelitis following dengue fever. J Infect Chemother 8: 175-177.

88. Tenembaum S, Chitnis T, Ness J, Hahn JS (2007) International pediatric MS study group. Acute disseminated encephalomyelitis. Neurology 17: 23-36.

89. Brito CA, Sobreira S, Cordeiro MT, Lucena-Silva N (2007) Acute disseminated encephalomyelitis in classic dengue. Rev Soc Bras Med Trop 40: 236-238.

90. Puccioni-Sohler M, Rosadas C, Cabral-Castro MJ (2013) Neurological complications in dengue infection: A review for clinical practice. Arq Neuropsiquiatr 71: 667-671.

91. Gupta M, Nayak R, Khwaja GA, Chowdhury D (2013) Acute disseminated encephalomyelitis associated with dengue infection: A case report with literature review. J Neurol Sci 335: 216-218.

92. Viswanathan S, Botross N, Rusli BN, Riad A (2016) Acute disseminated encephalomyelitis complicating dengue infection with neuroimaging mimicking multiple sclerosis: A report of two cases. Mult Scler Relat Disord 10:112-115.

93. Gera C, George U (2010) Acute disseminating encephalomyelitis with hemorrhage following dengue. Neurol India 58: 595-596.

94. Malheiros SM, Oliveira AS, Schmidt B, Lima JG, Gabbai AA (1993) Dengue. Muscle biopsy findings in 15 patients. Arq Neuropsiquiatr 51: 159-164.

95. Kalita J, Misra UK, Mahadevan A, Shankar SK (2005) Acute pure motor quadriplegia: Is it dengue myositis? Electromyogr Clin Neurophysiol 45: 357-361.

96. Misra UK, Kalita J, Syam UK, Dhole TN (2006) Neurological manifestations of dengue virus infection. J Neurol Sci 244: 117-122.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752