

Dengue Fever and Neurology: Well Beyond Hemorrhage and Strokes

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ABSTRACT

Dengue virus an arbovirus is endemic in an area that comprise almost half of the world's population, contrary to past beliefs that dengue virus differentiate from other neuroinvasive arbovirus due to its lack of neurological invasion and disease related neurological complications excluding hemorrhagic and thromboembolic , the body of evidence have grown to demonstrate a series of neurological manifestations linked to dengue virus with possible mechanisms involving direct virus invasion of the nervous system or immune mediated complications. In this review we provide a wide approach to this neglect but not so rare manifestations of a very common disease.

ABBREVIATIONS

dengue virus serotypes = DENV 1–4

dengue fever = DF

dengue hemorrhagic fever = DHF

cerebrospinal fluid = CSF

non-structural = NS

tumor necrosis factor = TNF

guillain-Barré syndrome = GBS

acute motor axonal neuropathy = AMAN

acute inflammatory demyelinating polyradiculoneuropathy = AIDP

Miller Fisher syndrome = MFS

creatine kinase = CK

Electromyography = EMG

acute disseminated encephalomyelitis = ADEM

magnetic resonance imaging = MRI

enzyme-linked immunosorbent assay = ELISA

transverse myelitis = TM

longitudinally extensive transverse myelitis = LETM

neuromyelitis optica spectrum disorders = NMOSD

New Daily Persistent Headache = NDPH

MANUSCRIPT

Introduction

Arboviruses are viral diseases transmitted by the bite of hematophagous arthropods, especially mosquitoes¹. These mosquitoes are vectors of diseases such as Dengue, Chikungunya, Malaria, Yellow Fever, and Zika virus. Its ability to transport and spread the disease to humans causes millions of deaths each year². In 2019 (by the end of October), Dengue alone registered 2.7 million cases worldwide, including 22,127 of severe cases and 1,206 deaths; 13% higher than the 2015 numbers - the year of the last outbreak³. Arboviruses have been a major public health challenge, especially with regard to disease control and its transmission chain.

Dengue is a mosquito-borne viral disease caused by one of four dengue virus serotypes (DENV 1–4), that are genetically similar but antigenically distinct^{4,5}. DENV is a small, spherical, lipid-enveloped viruses with a genome composed of a single-stranded, positive-sense RNA virus of the genus *Flavivirus*, family *Flaviviridae*^{6,7}. The disease is spread mainly by the female Mosquito *Aedes aegypti*, a vector that can be found in all tropical and subtropical regions, and by the Mosquito *Aedes albopictus*, in regions of temperate climate⁵.

The spectrum of symptoms caused by DENV infection range from an influenza-like disease known as dengue fever (DF) to a severe, sometimes fatal disease characterized by hemorrhage dengue hemorrhagic fever (DHF) and/or shock (dengue shock syndrome [DSS])⁸. DF symptoms included acute fever, headaches, muscle ache, joint pain, gastroenteritis, and skin rashes⁶. Less than 5% of patients progress to severe life-threatening

manifestations, usually seen in those who were previously exposed to heterotypic DENV infection⁷. In fact, the clinical outcome of dengue infection depends on several factors, both in the patient, in the vector, and in the virus itself⁹.

Interestingly, the dengue virus has also become a relevant agent for pathologies of the nervous system. Neurological manifestations in dengue virus-infected patients range from 0.5% to 21% in different studies⁴. The most common subtype associated with neurological disorders appears to be DENV-3¹⁰. In fact, in dengue disease, the hemorrhagic manifestations in the central nervous system (CNS) are the most known and reported in studies. However, here we discuss neurological manifestations apart from bleeding and heart attacks.

Search Methods

We searched PubMed for articles with no time restriction for articles published in English, using the term “dengue fever”, “myelitis”, “encephalitis”, “ADEM”, “new daily persistent headache”, “guillain barre syndrome”, “neurological complications”. We emphasized in clinical studies, case reports, systematic reviews with or without meta-analysis and pertinent narrative reviews to write this review treating about the neurological complications not caused by hemorrhagic or thromboembolic events. The articles selected for the discussion, with clinical data, in this review are presented in Table 1 with a short description of its main findings.

Discussion

Neurological events are uncommon, but an increase in these reports has occurred in recent years⁷. *Sahu and colleges* (2014) enrolled 486 patients and found an incidence rate of 9.26% of neurological complications in dengue fever patients¹⁰. Nonetheless, in a prospective study involving 116 patients, 79% of them presented some neurological complications: 34% presenting with encephalitis or encephalopathy, and 45% with muscular alterations¹¹. *Bhushan et al.* (2018) found 4.86% of immune-mediated neurological complications in 1627 patients with DENV infection¹². In children, a study with 71 confirmed cases showed that 28.17% of the patients had neurological involvement¹³. Another study evaluating 74 patients with possible viral associated neurological complications in Brazil found that 11% of those cases had relationship with DF¹⁴.

The pathogenesis of dengue involvement of the nervous system is not quite clear⁴. Such manifestations can result from the direct viral invasion of the nervous system due to its neurotropism, immune mediated mechanisms or vascular and metabolic abnormalities, as intracranial hemorrhage, cerebral edema, hyponatremia, hypokalemia, cerebral anoxia⁷.

In vitro and in vivo studies point to an involvement of glial cells and innate immune response in DENV infection^{15,16}, in one study with rhesus macaques there were no apparent brain histological alteration but a series of virus induced astrocytes alterations, decreasing its number, inducing its activation¹⁵. There is also evidence of the virus in the cerebrospinal fluid (CSF) of patients¹⁷.

In terms of the immune response, a study showed a similarity between the release of the cytokines in dengue infection and the Japanese encephalitis virus with several cytokines accumulated in the CSF, suggesting that inflammation can play an important role in dengue's CNS infection¹⁸. In this same context, *Al-Shujairi et al.* (2017) showed that TCD8 lymphocytes induced by the dengue virus in the CNS of mice, as well as genes stimulated by interferon indicating a virus drive immune response and inflammation¹⁹.

Neurovirulence may be due to some molecular specificities of some subtypes of the DENV virus. The evidence demonstrated in the dengue virus strain 1 shows a correlation between the domain of helicase E and non-structural-3 (NS3), increasing the capacity for infection and neuronal replication²⁰. There are also samples of replication of the DENV2 in neurons²¹. Another study in mice showed behavior similar to anxiety associated with an increase in inflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNF) and neuronal

loss in the hippocampus²². These findings are corroborated by another study with the dengue virus 3, inducing meningoencephalitis, and behavioral changes in mice²³.

Guillain-Barre Syndrome

Guillain-Barré syndrome (GBS), also known as acute idiopathic polyradiculoneuropathy, is an acute, inflammatory, demyelinating, and immune-mediated syndrome. The main findings are areflexia, ascending motor paralysis, and an elevated protein concentration, without pleocytosis (cytological albumin dissociation) in the cerebrospinal fluid⁴. In GBS 70% of the cases are preceded by respiratory or gastrointestinal infection, generally viral, 1 to 3 weeks before the onset of neurological symptoms. The microbiological agents most commonly involved with GBS are Cytomegalovirus, Epstein-Barr virus, *Campylobacter jejuni*, mycoplasma, and HIV^{24,25}.

GBS and its variants represent 5% of neurological complications in pediatric patients who had DF¹³, the period between the onsets of the illnesses of approximately 10,9 days²⁶. Acute motor and sensitive axonal neuropathy (AMSAN) was the most common GBS subtype in these patients, followed by acute motor axonal neuropathy (AMAN), acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and Miller Fisher syndrome (MFS)¹².

MFS is characterized by the triad of ophthalmoplegia, areflexia, and ataxia, which can also present bulbar paralysis in 60% of the cases. GBS and MFS are being linked as an immune-

mediated complication of DF²⁷. Another variant of GBS that has been reported with dengue disease is the pharyngeal-cervical-brachial variant²⁸.

In a interesting report, the axonal variant of the GBS has been described in two brothers simultaneously and associated with dengue virus infection although none of the two brothers had dengue fever typical symptoms²⁹, this report corroborates with a possible genetic predisposition associated with this complication of dengue.

As most cases of GBS occur after the acute stage of dengue, there is a tendency to believe that there is an immunological origin for such manifestations²⁷. This is because evidence supporting this hypothesis is related to the same pro-inflammatory substances that participate in both diseases, either in the immune response against the dengue virus or in the pathogenesis of GBS. TNF, interleukins, and complements are substances that might have an important role in the pathogenesis. Also, the immune response that needed to fight the dengue virus may cross-react (molecular mimicry) and attack myelin or peripheral nerve axons^{24,30}.

Myopathy

Myalgia is a well-known symptom of dengue disease. In some studies, 90% of the patients with dengue fever had myalgia as a complaint³¹. Muscular alterations in biopsy found 12/15 patients without muscle weakness complaints suggesting that muscular alterations occur even in asymptomatic patients³².

Myopathy is also a common presentation in dengue infection: 34 out of 116 patients presented with muscle weakness and high creatinine kinase serum levels¹¹. In another study

14 in 30 patients with acute myopathy had the diagnosis of dengue fever associated, 9 of those with normokalemia³³.

The severity and clinical presentation have great variation among patients with acute myopathy and dengue fever^{34,35}, varying from sub-clinical creatine kinase (CK) elevation to severe muscle weakness and even rhabdomyolysis or myocarditis can occur simultaneously with dengue acute myopathy^{11,34,35,36,37}. Electromyography (EMG) study when conducted does not show characteristics of inflammatory myositis^{34,38}.

The myopathy is usually self-limited and doesn't leave sequels^{34,38}. However, in 2006, *Finsterer and colleagues* described a case of a 38-year-old man that contract dengue fever on a holiday in Thailand and presented with fever, headache, and sore eyes associated with an intense 10/10 myalgia pain on a visual scale, which persisted for more than 60 days. Upon electromyography examination, the patient showed spontaneous activity in the subscapularis muscle. After 3 weeks of treatment with corticosteroids, the myositis resolved³⁹.

Encephalitis

While encephalopathy as a dengue fever manifestation is more commonly secondary to multisystem disorder from the infectious affection like shock, hepatitis, coagulation disturbs, and even concomitant bacterial infection; when it comes to encephalitis, this mechanism is different⁴⁰.

In the study of Bhushan et al. 9 patients out of the 79 with immune mediated neurological complications presented with acute disseminated encephalomyelitis (ADEM), 3 had

cerebellar demyelination only and 1 patient had limbic encephalitis ¹². Considering these three manifestations, 0,8% of the patients with dengue fever had encephalitis associated with dengue virus infection a higher number was found in a pediatric study although with a smaller sample n=71 patients, 8% of those children had encephalitis related with dengue fever and another interesting data was that of those 4 children that died 3 of them had encephalitis ¹³.

Although rarer, dengue encephalitis is due to direct neuronal infiltration, inducing the neurological riot by the virus itself in immunological means ^{40,41}. Whilst Dengue is not considered a neurotropic virus, there are increasing evidences that concern this component in encephalitis ⁴⁰. It mainly occurs once the encephalopathy is not regarding to other dengue features, and when the CSF contains the dengue virus and IgM antigen ⁴². Also, the encephalitis take place in the viremic stage of the disease, while other encephalopathies happen later. There is evidence that implies the DENV-2 and DENV-3 as the serotypes most verified in neurotropism ⁴³.

In cases that encephalitis is presented, the manifestation comprises from headache, confusion, dizziness, disorientation, behavioural symptoms and drowsiness ⁴. Occasionally, reaching cranial nerve palsy, diminished deep tendon reflexes, leading to hypotonia and hemiparesis. Seizures are not infrequently seen and the neurological affection can attain up until coma ⁴³. It may be accompanied by fever, arthralgia, myalgia, and vomiting, typical dengue symptoms. There might be leukopenia, thrombocytopenia and peripheral blood according to viral infection as well ⁴³.

For this diagnosis, some criteria are needed. As established by *Carod-Artal et al.* (2013), it is necessary the existence of clinical signs and symptoms of CNS injury, dengue virus RNA,

IgM or NS1 antigen testing positive in CSF and CSF lymphocytic pleocytosis without other neuroinvasive pathogens by testing negative for other possible infectious diseases⁴.

Succeeding this assay, Soares and colleagues, in a supplementary study, proffered as definition of dengue encephalitis the presence of fever, associated to acute signs of cerebral involvement, reactive IgM antibody, NS1 antigen or positive dengue PCR on serum and/or CSF, as well as the exclusion of other viral encephalitis causes and encephalopathy⁴⁴.

Neuroimaging in dengue virus encephalitis shows no disturb in most cases⁴⁵. Yet, once the affection is verifiable via magnetic resonance imaging (MRI), it is commonly demonstrated as abnormal multifocal hyperintensity in MRI T2W and MRI FLAIR sequences in both hemispheres, periventricular zones, including basal ganglia^{43,46}. Some peculiar patterns had been associated with dengue encephalitis on the MRI, as the “double doughnut sign” and the “Jack-o'-lantern-sign”, in light of the bilateral nature of the lesions⁴⁷⁻⁴⁹. Furthermore, the involvement of brainstem, cerebellum, corpus callosum and bilateral thalami is shown as possible in some patients, being the affection present in both white and gray brain matter⁴⁵.

Though not specific, the electroencephalogram (EEG) might present generalized slow waves in encephalitis, despite of being often imputable to seizures, intracranial hemorrhage and viral infection⁴³.

As concerns to laboratory analysis, dengue NS-1 antigen trial has to be positive in serum. CSF was described as colorless and clear in most cases, also presenting lymphocytic pleocytosis and testing negative for other infectious serology^{42,43}. IgM testing in the CSF by enzyme-linked immunosorbent assay (ELISA) for dengue antibody, which has both high sensitivity (92%) and specificity (99%), is widely applied and reliable in this diagnosis

investigation^{43,46}. The gold standard would be the isolated virus in cell culture with antibody identification by fluorescence, however, the appliance of this method is scarcely available⁴⁶.

It is equally important testing the serum and CSF for herpes simplex virus, *Mycobacterium tuberculosis*, cytomegalovirus, human T cell lymphotropic virus type-1, Epstein-Barr virus and varicella zoster virus in order to decline this potential causes once the respective results are negative¹².

Moreover, the encephalitis must be distinguished from encephalopathy of other etiology, in which the detection of dengue virus, NS1 antigen or IgM dengue virus-specific antibodies in CSF will cooperate⁴. Nonetheless, other probable infectious disease testing negative is important to differential diagnosis. Through the CSF sample, it is possible to verify the presence or absence of Japanese encephalitis virus IgM, whereby it is proven or rejected the Japanese Encephalitis hypothesis, that is one of the main differential options⁵⁰. Always aware to the possibility of cross-reactivity and considering the epidemiology context, the PCR exam is able to determine the concomitant infection of both viruses⁵¹.

In the matter of treatment, although there is no effective antiviral agent for dengue virus, acyclovir, corticosteroids and sodium valproate are occasionally used in dengue encephalitis management⁴³. Despite that, the supportive care is always necessary, in which antipyretic drugs, analgesics and oral fluids might be useful. On the other hand, it is contraindicated the use of most non-steroidal anti-inflammatory, mainly acetyl-salicylic derivatives⁴.

Post-mortem analysis exhibit that the predominant features found of these patients' brains consists in non-specific oedema lesions⁴. In cases the autopsy was performed, the

histopathological patterns were cerebral edema, vascular congestion, hemorrhage, perivascular lymphocytes infiltration, inflammation and also brain matter necrosis^{4,43, 52}.

Through immunoperoxidase stain it may as well be verified the virus antigen in brain parenchymal cells⁴³.

Myelitis

Spinal cord involvement, especially in the form of Transverse Myelitis (TM), is not a common manifestation of dengue virus infection, but it is not ignorable. In a study conducted by *Sahu et al.* (2014) 45 out of 484 patients developed neurological complications, of this, 7 had myelitis resulting in a 1.4% incidence¹⁰. Additionally, in a study with 1627 patients with 79 presenting neurological immune-mediated syndrome 9 patients had acute disseminated encephalomyelitis and 5 had just myelitis¹². In children, 5% of the patients studied by *Sil et al.* (2017) had myelitis associated with dengue infection¹³.

When present, TM may be associated with difficult clinical recovery conditions that often promote long-term disability⁵³. When a spinal injury affects more than 3 vertebral segments, the disease can be defined as Longitudinally Extensive Transverse Myelitis (LETM), an even rarer condition which leads to severe morbidity⁵⁴.

Some related symptoms to TM are weakness or paralysis of upper and lower limbs, urinary retention, and sensory alterations⁵⁵. It is proposed that temporal factors play a significant role in pathology presentation, considering that in the acute phase patients mainly manifest flaccid paralysis, and in the post-infectious stage, which can begin 1-2 weeks after the initial symptoms, they usually present spastic weakness^{56,57}.

According to *Mota et al.* (2017), the initial signs of TM associated with DF may be twofold. First, due to the direct viral action on the spinal cord; later, the disease's effects may result

from an immune reaction ⁵⁸. Direct viral invasion diagnosis is supported by IgG and IgM tests or by isolating the virus at very early stages in CSF ⁵⁹. A retrospective study involving 10 patients with DF's neurological complications revealed that 7 of them had positive IgM antibodies and 9 were IgG positive for dengue virus in CSF ⁶⁰. The detection of high protein and leukocyte levels in the CSF could indicate an acute inflammatory process due to the viral local effect, as well ⁶¹. Some diagnostic imaging methods such as MRI can also be performed to detect signs of inflammation and for differential diagnosis ⁵⁷.

Also, a 2018 report of two patients with neuromyelitis optica spectrum disorders (NMOSD) positive for aquaporin-4 antibodies associated that open the clinical picture of NMOSD concomitant with an acute dengue fever infection ⁶².

There are still controversies about TM's treatment decisions. Even with proper therapy, many patients take months to restore neurological functions, and some of them remain with residual symptoms. There is no high-level evidence to support the use of intravenous corticosteroids, however, pulse therapy with methylprednisolone is still the main option. Therapeutic plasma exchange can also be used as a second choice ⁵⁷. A case report of a 24-year-old woman, who tested positive for dengue IgM/IgG antibodies and presented acute myelitis, showed that even being treated with IV pulse methylprednisolone immunoglobulin plasmapheresis and physiotherapy, it was not possible to obtain a complete recovery in her motor and sensory deficits after 5 months ⁶³.

Even though myelitis is rarely associated with DF, it is important that clinicians are aware of its existence as a possible complication of the disease, to investigate it in the face of neurological symptoms in patients typical dengue symptoms ⁵⁶.

Acute disseminated encephalomyelitis

As previously approach, myelitis and encephalitis can be individual entities in the dengue fever neurological complications spectrum disorders. Another neurological complication linked to dengue fever ADEM present with both encephalitis and myelitis signs.

Bhushan and colleagues found that 11% of the patients with dengue fever immune mediated neurological complications had ADEM¹², in another study Sil et al. evaluating a pediatric population found 5% of pediatric patients with dengue fever neurological complications had ADEM associated to¹³. A meta- analysis of 2017 encountered a prevalence of 0.4% of ADEM among dengue fever patients⁶⁴.

The onset of neurological manifestations ranged from 3 to 19 days after the first symptoms the most common neurological manifestations was: altered mental status (58%); seizures and urination problems (35%); vision problems (31%); slurred speech (23%); walking problems (15%) and ataxia (12%)⁶⁴. In Kamel study there are few informations on the spinal MRI of the patients but of 9 patients with ADEM in Bhushan research's 7 had a LETM as a featured in image study's¹², another review that presented 22 cases points to these same direction stating that most patients had extensive myelitis with preference to the cervical and thoracic segment⁶⁵.

More recently 3 peculiar cases of ADEM associated with dengue fever had been described. Firstly, a patient with a 5-day history of fever that was found in a post vital state by its sister and presented in the emergency service with Glasgow coma scale of 5 needing mechanical ventilation, he was later treated with intensive care and steroids and recovered⁶⁶. The other 2 cases showed two patients with dengue fever associated ADEM presenting with MRI images mimicking multiple sclerosis⁶⁷.

Treatment used, varied from intravenous immunoglobulin, steroids, plasmapheresis and other immunotherapy^{64,65}. In terms of prognosis of the 29 cases analyzed in Kamel et al. meta-analysis 3 patients died, 7 had partial recovery and 16 had complete recovery. Patients with complete recovery had lower body temperature when compared to the partial recovery group and bad outcome group⁶⁴.

New Daily Persistent Headache

New Daily Persistent Headache (NDPH) is a primary headache of abrupt onset and daily persisting without remission⁶⁸. Although viral infections, surgical procedures, and stressful lives are punctuated as triggers, the pathogenesis remains unclear⁶⁹. Studies have already shown an association between EBV infection and NDPH⁶⁸. Admirably, the association between dengue and NDPH was also recently described^{69,70}. *Abreu et al. (2019)* reported 450 patients with dengue and NDPH, with a prevalence of 0.67% (3 patients), which is higher than the estimated prevalence of 0.03-0.1% in the general population⁶⁸.

In 2017, *Bordini and colleagues (2017)* reported two cases of NDPH after dengue fever. The first one was a 23-year-old Caucasian male with a two-year history of daily headache. Pain was bilateral, in pressure, and severe in most of the time. Also, it was refractory to Amitriptyline, Divalproex, and Topiramate; and temporary relief was obtained after nerve blockade. The second one was a 42-year-old caucasian woman that presented with bilateral pressure headache the week after the onset of dengue fever (with positive serology). Pain was moderate to severe and nausea, photophobia and phonophobia also occurred. Pain persisted for the next seven months, but relief was obtained with a 10-day course of dexamethasone⁶⁹.

Others

The “others” neurological manifestations of dengue fever deserve a review on its own due to the plurality of disorders associated with the virus in the literature. In fact, these unusual associations range from rapid progressive dementia in an elderly patient⁷¹ until dengue-associated psychiatric illness, as a case of manic symptoms reported in India⁷². In this same context, this time in Saudi Arabia, two other patients developed recurrent migraine-like attacks associated with a terrifying feeling of near-death phobia in conjunction with signs of dysautonomia, after viral meningitis due to Dengue⁷³.

On the spectrum of movement disorders, *Misra & Kalita (2010)* found that 11% of patients with dengue encephalitis had movement disorders⁷⁴. There are also reports of parkinsonism associated with dengue involving adults and pediatrics patients^{75,76}. Other neurological presentations associated with DENV infection are opsoclonus-myoclonus^{77,78}, cerebellar syndrome⁷⁹, and ocular flutter with truncal ataxia⁸⁰.

These more varied presentations of the disease still include multiple motor neuropathy responsive to intravenous immunoglobulin⁸¹, isolated cranial paralysis^{82,83}, neuralgic amyotrophy that took 3 months to recovery in 2 out of 3 patients in a case series⁸⁴, immune-mediated cauda equina syndrome in a European patient after a trip to Brazil with positive CSF for IgM antibodies to dengue, as well as oligoclonal bands⁸⁵, a case of hemiconvulsion hemiplegia triggered by dengue infection⁸⁶ and 2 patients presented in Bhushan and colleagues study with a painful retrobulbar optic neuritis¹².

Conclusion

In conclusion, it is important to clarify that dengue fever is not an emerging infectious disease but a well-established illness with almost half of the world's populations living in endemic areas and susceptible to the virus.

In addition to what was believed, the dengue virus has a diverse number of associated neurological complications, which are not necessarily correlated with hemorrhagic or thrombotic events, as seen briefly in this review. The diagnosis is made by routine cerebrospinal fluid (CSF) test, which shows an inflammatory reaction, protein-cytological dissociation, cerebromeningeal bleeding in some cases or ischemic stroke, presence of specific viral antigens and/or antibodies and exclusion of other infectious diseases⁷.

In endemic areas, especially in the most important contagion seasons such as summer, an unresolved neurological case, the diagnosis of dengue should not be ruled out. The disease must be considered, tested, and properly managed. This is because dengue can present with severe neurological conditions, but which can follow self-limited processes and with a good prognosis.

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TABLE 1

Author	Year	Country	N	Main Findings
Prevalence				
Bhushan et al. ¹²	2018	India	1627	In this cross-sectional observational study, 1627 laboratory-confirmed DF cases, 14,6% presented neurological complications, and 4,86% (79) had immune-mediated neurological complications. The spectrum of IMNC included GBS, MFS, ADEM, myelitis, polyneuritis cranialis, among others, and the majority of these developed in a subacute period (7-30 days). GBS was detected in 32 cases, with acute motor and sensory axonal neuropathy subtype being the most prevalent, 18 patients. They also had 3 patients with MFS. Out of 32 patients, 25 had a full recovery with the treatments that varied from immunoglobulins, plasmapheresis and methylprednisolone.
Sil et al. ¹³	2017	India	71	It's a descriptive, observational, cross-sectional study that analyzed 71 children with the age range of 1–12 years. 28% had neurological involvement, encephalopathy (40%), encephalitis (30%), pure motor weakness (15%), TM (5%), ADEM (5%), GBS (5%), were the the common presentations.
Encephalitis				
Chatur et al. ⁴⁸	2019	India	2	Two dengue encephalitis cases showing the “double doughnut sign” in reference to symmetric involvement of bilateral CNS parenchyma.
Weerasinghe et al. ⁴³	2019	Sri-Lanka	1	A case report of a 18-year-old patient that had a encephalitis associated with DHF.
Kyaw et al. ⁵⁰	2019	Myanmar	123	The study was designed to evaluated the weight of Japanese encephalitis virus and DENV in children under 13 on Myanmar. They found 1 patient with dengue fever among the 123 patients.
Singh et al. ⁴⁹	2018	India	1	The Jack-o'-lantern sign in a patient that with dengue encephalitis that died on day 7.
Jois et al. ⁵²	2018	India	3	Viral neurotropism may occur in DF causing direct neuronal damage, generating viral encephalitis. Autopsy findings were cerebral edema with obliteration of the sulci and flattening the gyri. The dura was found tense and there were hemorrhagic foci all over the brain. Microscopically, cerebral edema, inflammation and hemorrhage were the main findings. All three patients were positive for NS-1 dengue antigen.
Kumar et al. ⁴⁷	2017	India	1	A 22-year-old primagravida that had encephalitis associated with DF. On the MRI she had lesions with the appearance of double doughnut sign.

Kutiyal et al. ⁴⁶	2017	India	1	A case report with a brain MRI on T2 weighted and FLAIR sequence showing hyperintense lesions in bilateral ganglio-thalamic complex, periventricular and peritrigonal white matter on Dengue encephalitis.
Garg et al. ⁴⁵	2017	India	1	Involvement of brainstem, cerebellum, corpus callosum and thalamus in dengue encephalitis, evidences with multifocal hyperintensities in bilateral periventricular zones, including basal ganglia, in T2W and FLAIR sequences.
Sivamani et al. ⁵¹	2017	India	1	A patient with encephalitis that had both DENV and Japanese encephalitis virus serology positive, but the authors were to realize the PCR to confirm if it was a dual infection or a cross reactivity.
Withana et al. ⁴¹	2014	Sri-Lanka	1	A case of acute cerebellitis associated with de hue fever. Dengue antigen is demonstrated in the brain of patients with dengue encephalitis
Rao et al. ⁴⁰	2013	India	1	A dengue encephalitis case with positive antibodies and antigen testing on the CSF of the patients.
Soares et al. ⁴⁴	2014	Brazil	Not applied	New propose for dengue encephalitis definition: (1) presence of fever (2) acute signs of cerebral involvement, such as altered consciousness or personality and/or seizures and/or focal neurological signs (3) reactive IgM dengue antibody, NS1 antigen or positive dengue PCR on serum and/or CSF, according to the time of onset (4) exclusion of other causes of viral encephalitis and encephalopathy.
Borawake et al. ⁴²	2011	India	1	A case of DENV associated encephalitis described.
Guillain-Barre Syndrome				
Silva et al. ²⁷	2019	Sri Lanka	1	GBS and its variants usually develop after 1 or more weeks of the acute infection, which suggest an immunological ground. The dengue virus has a potential neurotropism for peripheral nerves that cause illness. In their case, the MFS was assumed to be a parainfectious manifestation, not a postinfectious
Pandey et al. ²⁸	2019	India	1	A case report of a pharyngeal-cervical-brachial variant of GBS associated with dengue fever infection.
Pandey et al. ²⁹	2018	India	1	A report of two brothers presenting simultaneously with an Axonal variant of GBS both associated with a mild dengue fever infection, the author calls attention for the possible genetic mechanism associated with GBS and dengue fever.

Dalugama et al. ²⁴	2018	Sri Lanka	1	It suggests that screening for dengue in patients with acute flaccid paralysis may be important in hyperendemic regions. The article discusses about the correlation and the pathogenesis of GBS and dengue fever. It postulated about two possible mechanisms, one being the molecular mimicry, that is when the cell-mediated immunological response to nonself-antigens misdirect to the host nerve tissue. And the other one, is that pro-inflammatory cytokines (TNF, complements, and interleukins) that participated in the immune response of dengue fever may have an important role.
Fragoso et al. ²⁶	2016	Brazil	10	These report 10 cases of DF and GBS, with variable and severe symptoms, and acute motor-sensory axonal neuropathy being identified in all cases. The average days between DF and GBS was 10,9 days. All patients were treated equally with immunoglobulin, and full recovery varied from nine days to one year.
Simon et al. ⁶	2016	New Caledonia	3	It reports 3 cases of early GBS and dengue fever. All these three patients had de neurological disease and its regression, dengue fever, and the serum diagnosis within one week, suggesting an infectious origin. Contrasting with the majority of the cases, which are considered as a post-infectious disease.
Ralapanawa et al. ³⁰	2015	Sri Lanka	1	It reports a case of a 34 years old man who had DF and 10 days later developed GBS. He has treated with plasmapheresis and recovery well. They discuss the mechanism for GBS after DF, being an immune-mediated neurological disease in which DF response, with pro-inflammatory substances, may have an important part.
Gonçalves et al. ²⁵	2011	Brazil	1	It reports a case of a six years old girl who had DF and 20 days later developed GBS. She was treated properly but some neurological sequels remained. It tries to explain the correlation in the pathogenesis between these two diseases, being the main factor the similarity of the immune response presented by both.
Myopathy				
Verma et al. ³³	2017	India	30	In this observational study, 14 out of 30 patients presenting creatinine kinase (CK) elevation were caused by dengue infection of this 5 with hypokalemia and 9 had normokalemia. Those with normokalemia were more prone to have CK 10 times the normal value compared with the hypokalemic group.
Misra et al. ¹¹	2015	India	116	In this prospective study, 79% out of the 116 patients analyzed presented a neurological complication. 34% presented with encephalopathy or encephalitis and 45% had muscle dysfunction of those 34 patients had muscle weakness associated with high CK levels, 97% of patients with muscle weakness had myalgia. Muscle weakness were severe in 20 patients and 16 patients had hyporeflexia.

Kalita et al. ³⁸	2012	India	13	13 patients with dengue myopathy were submitted to electromyography (EMG) and a 1 month follow up. The weakness was more prominent proximal and in the lower limbs. There was no difference in EMG between the severe and mild group, none of the groups show signs characteristic of inflammatory myopathies.
Misra et al. ³⁴	2011	India	39	In this study 16 patients had muscle weakness and high CK level and 15 had just higher CK levels without muscle weakness. 8 patients presented severe muscle weakness and 5 had hypotonia and hyporeflexia. By 2 weeks all patients presented full recovery. Electromyography didn't show characteristics of inflammatory myopathy and the 3 patients that underwent muscle biopsy didn't show myositis either.
Paliwal et al. ³⁵	2011	India	7	In this case series it's described a great variety of clinical presentations of dengue myositis, from mild asymmetric weakness for severe 3 cases of fulminant myositis.
Acharya et al. ³⁶	2010	India	1	A case report of a 40-year-old man presenting with fever and myalgia with muscle tenderness and pain to movement but normal strength. In the next day he presented flaccid quadriparesis which progressed to pharyngeal muscle weakness, head drop and respiratory insufficiency and rhabdomyolysis. A muscular biopsy showed perifascicular myonecrosis.
Sangle et al. ³⁷	2010	India	1	A case report of a 16-year-old girl that had myositis and myocarditis associated with dengue infection.
Finsterer et al. ³⁹	2006	Austria	1	A case report of a 38-year-old man that experience severe headache and fever on a holiday in Thailand, that was followed by a severe myalgia 10/10. After 36 days he still had 6/10 myalgia and electromyography revealed electrical spontaneous activity on the subscapularis muscle. 62 days after the onset he received dexamthasone for 3 weeks resolving the pain.
Malheiros et al. ³²	1993	Brazil	15	The study shows perivascular infiltrates in 12 out of 15 patients with acute classic dengue fever but there was no sign of myositis. None of the patients had alterations on the neurological exam and just 3 had abnormal CK levels on serum.
Myelitis				
Landais et al. ⁶³	2019	France	1	This case report describes a 24-year-old woman who developed myelitis on the 7th day of dengue fever. Spinal MRI identified diffuse medullary hyperintense lesions, suggesting acute inflammation. She was treated with intravenous pulse methylprednisolone, immunoglobulin plasmapheresis and physiotherapy, achieving almost full recovery after 5 months.

Chaudhry et al. ⁵⁵	2018	India	1	This case describes a 55-year-old woman who tested positive for dengue IgM antibody, and who developed spontaneous subarachnoid hemorrhage and LETM. She was properly treated with methylprednisolone pulse therapy and physical therapy, but after a one-month follow-up, the patient didn't show any significant signs of recovery.
Malik et al. ⁵⁷	2018	India	1	It describes a case of an adolescent patient who presented symptoms of TM after 4 weeks of DF. The authors discuss the difference between acute (parainfectious) and late (post-infectious) stages of dengue with neurological manifestation and suggest that the parainfectious phase is characterized by direct infection of dengue virus in the spinal cord but, at the post-infectious one, immune reactions play the main role.
Lana-Peixoto et al. ⁶²	2018	Brazil	2	Two patients with NMOsD that occur associated with DF infection, both patients tested positive for AQP4 antibodies.
Mota et al. ⁵⁸	2017	Brazil	1	This article reports a case of a 21-year-old male patient who had dengue fever and manifested TM. The authors discuss the real prevalence of dengue-associated TM, suggesting that is underestimated and reinforcing the importance of careful evaluation and follow-up to avoid misdiagnosis.
Fong et al. ⁵⁴	2016	Malaysia	1	This article reports the first pediatric case of LETM associated with DF. A 12-year-old girl presented flaccid quadriplegia on the 8th day of dengue infection. She was treated with pulse methylprednisolone, intravenous immunoglobulin, and plasmapheresis, reaching an almost complete clinical recovery after six months, persisting with mild residual weakness of her limbs.
Tomar et al. ⁵⁶	2015	India	1	In this article, a case of a middle-aged man, who developed LETM in the acute parainfectious phase of DF. On the third day of fever, the patient started presenting neurological alterations such as lower limb weakness, urinary retention, and sensory impairment. Although this disease is associated with a poor prognosis, the patient achieved total improvement in neurological symptoms without residual deficits, receiving treatment with intravenous corticosteroids.
Larik et al. ⁵³	2012	India	1	This article describes a case of an adolescent male patient with high-intensity low back pain who was diagnosed with LETM 4 weeks after dengue's infection onset.
Chanthamat et al. ⁵⁹	2010	Thailand	1	This case describes a 61-year-old woman who developed acute paraplegia with sensory loss and urinary retention 6 days after the onset of DF. She was diagnosed with TM and received immunomodulatory treatment, achieving complete recovery after one month.

Puccioni-Sohler et al. ⁶⁰	2009	Brazil	10	This retrospective study analyzed 10 patients with the age range of 22 to 74 years and with IgM/IgG seropositivity for dengue, who developed neurological symptoms. Three of them were diagnosed, by spinal MRI and CSF inflammatory findings, with Transverse Myelitis. In one of the patients, it was also identified intrathecal synthesis of dengue antibodies in CSF, which could be associated with direct viral invasion of the spinal cord.
Soares et al. ⁶¹	2006	Brazil	13	This retrospective study involved 13 patients, 10 women and 3 men between 11 to 79-years-old, who developed DF during the epidemic of 2002 in Rio de Janeiro and who had neurological complications. Two of them manifested myelitis with paraparesis and sphincteric retention, but MRI results were abnormal in only one of the cases. According to CSF analysis, both of them had elevated Albumin Quotient (which could mean blood-CSF barrier dysfunction), and one had intrathecal synthesis of antibodies. High levels of cells and protein in the CSF were also defined as indicators of direct viral invasion and acute inflammation, and were present in both cases.
ADEM				
Rastogi et al. ⁶⁶	2019	India	1	A case report of a man with ADEM associated with dengue fever that rapidly progress to respiratory insufficiency requiring mechanical ventilation, but presented food response to cortical steroids.
Sulaiman et al. ⁶⁵	2017	Review	22	A narrative review with a summary of 22 cases of ADEM Associated with dengue fever.
Kamel et al. ⁶⁴	2017	Meta-analysis	29	In this meta-analysis the authors found a 0.4% prevalence of ADEM in dengue fever patients, corresponding for 6.8% of all neurological complications in DF.
Viswanathan et al. ⁶⁷	2016	Malaysia	2	Two cases of ADEM associated with DF that mimicked multiple sclerosis on the neuroimaging.
New Daily Persistent Headache				
Abreu et al. ⁷⁰	2020	Brazil	450	Of 600 cases of dengue fever in the city, the authors were able to contact 450. Of these 450 patients, 3 cases of NDPH were confirmed, leading to a prevalence of 0.67% (1:150) of NDPH attributed to dengue fever.
Bordini & Valença ⁶⁹	2017	Brazil	2	Two cases were reported. Case 1: 23 years old Caucasian male with a two-year history of headache. Pain was bilateral, in pressure, and severe most of the time. It was refractory to amitriptyline, divalproex and topiramate. Nerve blockade led to temporary relief for 2 weeks. Case 2: 42-years old Caucasian woman with bilateral pressure headache, moderate to severe, sometimes associated to nausea, photophobia and phonophobia; with substantial relief after the use of dexametasone for 10 days

Others				
Mohammed et al. ⁷¹	2020	India	1	A case report of a 64-year-old woman that presented with a rapid progressive dementia associated with focal epilepsy a month after a uncomplicated dengue infection. The autoimmune conditions research was negative, she had a normal MRI. She received intravenous corticosteroids and gradually improved within 4 weeks.
Borrelli et al. ⁸⁵	2019	Belgium	1	A case report of a 35-year-old woman that presented fever, myalgia, pain in the eyes, arthralgia after a trip to Brazil. 2-months later she had cauda equina syndrome and received the diagnosis of immune mediated sacral radiculitis associated with dengue fever. She had positive IgM-antibodies for dengue on the CSF as well as oligoclonal IgG bands.
Sardana et al. ⁸²	2019	India	1	A case of facial nerve palsy associated with dengue fever infection.
Desai et al. ⁷⁷	2018	India	1	A case report of a 14-year-old boy with dengue fever that developed opsoclonus myoclonus with spontaneous resolution in 2 weeks.
Higgoda et al. ⁸¹	2018	Sri Lanka	1	A case of multiple motor neuropathy associated with dengue fever infection that responded well with immunoglobulin therapy.
Saini et al. ⁸⁶	2017	India	1	A case of hemiconvulsion hemiplegia epilepsy triggered by dengue virus infection.
Mahale et al. ⁸⁰	2017	India	1	A case report of a 14-year-old boy with ocular flutter and truncal ataxia with concomitant dengue fever infection. He was treated with corticosteroids and the ocular flutter and ataxia improved.
Jaganathan et al. ⁸³	2014	India	1	A case report of an isolated hypoglossal nerve paralysis associated with dengue virus infection.
Weeratunga et al. ⁷⁹	2014	Sri Lanka	3	The authors described three cases of cerebellar syndrome related to dengue infection, with positive IgM against dengue virus on the CSF.
Fong et al. ⁷⁶	2014	Malaysia	1	A case of pediatric post-dengue encephalopathy parkinsonism in a 6-year-old patient that took 7-weeks to regain its normal function.
Tan et al. ⁷⁸	2014	Malaysia and Myanmar	2	Two cases of opsoclonus of myoclonus with dengue infection. The first in a 30-year-old adult that had a pachy- and leptomeningeal enhancement. The second case happened in a 10-year old child with normal EEG and computed tomography, MRI wasn't realized in this case.

Mamdouh et al. ⁷³	2013	Saudi Arabia	2	Two cases of atypical meningitis due to dengue virus with the patients presenting recurrent migraine like attacks, phobia (terrifying sense of near death) and signs of cardiac dysautonomia.
Srivastava et al. ⁷²	2013	India	1	A case report of a 21-year-old without family history or other risk factors, that developed maniac symptoms after a dengue fever infection.
Azmin et al. ⁷⁵	2013	Malaysia	1	A 18-year-old men that developed parkinsonism associated cerebellar ataxia, multiple cranial neuropathies and brachial plexopathy- that resulted in denervation on eletromyography after one month of onset. This presentation was following a dengue fever infection.
Verma et al. ⁸⁴	2011	India	3	A case series of patients that developed neuralgic amyotrophy associated with dengue infection, 2 patients just showed up complete recovery of strength at the third month of follow up.

Table 1. We summarize all the case reports, clinical studies and pertinent reviews we utilized to show DF neurological phenotype in the discussion

Appendix 1: Authors

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