Neurodengue, a narrative review of the literature

Neurodengue, uma revisão narrativa da literatura

Abelardo Queiroz Campos Araujo[1,2] Marco Antonio Lima[1,3] Marcus Tulius Teixeira Silva[1,4]

[1] Fundação Oswaldo Cruz, Instituto Nacional de Doenças Infecciosas, Laboratório de Pesquisa Clínica em Neuroinfecção.
[2] Universidade Federal do Rio de Janeiro, Instituto de Neurologia Deolindo Couto, Rio de Janeiro RJ, Brazil.
[3] Universidade Federal do Rio de Janeiro, Seção de Neurologia, Rio de Janeiro RJ, Brazil.
[4] Complexo Hospitalar de Niterói, Departamento de Neurologia, Niterói RJ, Brazil.

Address for correspondence Abelardo Q. C. Araujo (e-mail: abelardo@ufrj.br).

Arq. Neuro-Psiquiatr. 2024;82(7):s00441787799.

Abstract

Dengue fever (DF) is the most frequent arboviral disease globally. Deforestation, armed conflicts, and climate change have caused an unprecedented global spread of DF, raising concerns in healthcare systems worldwide. Systemic manifestations of the disease range from mild to severe and, in some cases, can lead to death. Although neurological complications have been reported over the last few decades, they are often neglected or underreported. The present narrative review aims to describe the most important central and peripheral nervous system complications and provide guidance to neurologists in terms of diagnosis and management.

Keywords
- Dengue
- Arboviruses
- Brain
- Nervous System
- Neurologic Manifestations

Resumo

A dengue é a arbovirose mais frequente no mundo. O desmatamento, os conflitos armados e as mudanças climáticas levaram a uma disseminação global e sem precedentes da dengue, o que gera preocupações na maioria dos sistemas de saúde em todo o mundo. As manifestações sistêmicas variam de leves a graves, incluindo morte. Complicações neurológicas têm sido descritas nas últimas décadas, mas geralmente são negligenciadas ou subnotificadas. O objetivo desta revisão narrativa é descrever as complicações neurológicas centrais e periféricas e auxiliar os neurologistas em seu diagnóstico e manejo.

Palavras-chave
- Dengue
- Arbovírus
- Encéfalo
- Sistema Nervoso
- Manifestações Neurológicas

INTRODUCTION

Neurologists are occasionally faced with epidemic infectious diseases that can cause neurological symptoms, such as severe acute respiratory syndrome (SARS), zika virus infection, and chikungunya fever.[1,2] Previous outbreaks have resulted in a high rate of neurological sequelae, and dengue fever (DF) is the latest cause for concern.[3]

received
March 11, 2024
received in its final form
April 29, 2024
accepted
May 1, 2024

DOI https://doi.org/10.1055/s-0044-1787799.
ISSN 0004-282X.

Editor-in-Chief: Ayrton Roberto Massaro.
Associate Editor: Paulo Pereira Christo.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

The present review aims to provide a critical and narrative assessment of DF and its neurological complications. To achieve this, research was conducted on the PubMed/MEDLINE, Web of Science, and Scopus databases using free-text words and terms related to the following medical subject headings (MeSH) terms: *dengue virus*, *brain*, *encephalopathy*, *encephalitis*, *dengue hemorrhagic fever*, *neurological manifestations*, *nervous system diseases*, *central nervous system diseases*, *encephalitis*, *meningitis*, *Guillain-Barré syndrome*, *acute inflammatory demyelinating polyneuropathy*, *myelitis*, *myositis*, and *myopathy*. We selected and reviewed original studies published in English online until March 1st, 2024. The final reference list was created based on each paper's relevance to the scope of the present review.

After malaria, DF is the second most significant disease spread by mosquitoes. It can cause a variety of symptoms, ranging from minor fever, headache, and muscular aches to severe hemorrhagic fever that can be fatal.[4] The dengue virus (DENV) has four distinct serotypes: DENV1 through DENV4. Of these, the "Asian" DENV2 and DENV3 genotypes are usually linked to severe illness that coexists with subsequent dengue infections.[5,6]

Recently, the World Health Organization[4] (WHO) reviewed the clinical recommendations for DF, and central nervous system (CNS) involvement is now included in the classification of severe DF. In areas where DF is prevalent, a diagnosis of severe DF should be considered if the patient presents with fever for 2 to 7 days in addition to any accompanying symptoms, as seen in ►**Table 1**.

An increasing number of DF cases have been observed in many places of the world. ►**Figure 1** shows a broad perspective of the regions in the world with a higher occurrence of DF. To obtain regularly-updated data, visit the WHO website (https://www.who.int/emergencies/disease-outbreak-news). The WHO estimates that 4 billion people are at risk for *Aedes*-borne infections.[7] In all 6 WHO regions, more than 5 million cases of DF and more than 5 thousand deaths have been linked to the disease since the beginning of 2023. Deforestation, armed conflicts that disrupt local health systems and delay access to healthcare, and climate

Table 1 Clinical characteristics of severe dengue fever

Accompanying symptoms	Comments
Evidence of plasma leakage	High- or progressively-rising hematocrit, pleural effusions or ascites, circulatory compromise, or shock
Significant bleeding	With or without externalization
Altered level of consciousness	Lethargy or restlessness, coma, convulsions
Severe gastrointestinal involvement	Persistent vomiting, increasing or intense abdominal pain, jaundice
Severe organ impairment	

Figure 1 World distribution of dengue fever cases (WHO, 2009).[4]

Table 2 Clinical stages in dengue fever

Febrile stage	Dehydration; high fever may cause neurological disturbances and febrile seizures in young children
Critical stage	Shock from plasma leakage; severe hemorrhage; organ impairment
Recovery stage	Hypervolemia (only if intravenous fluid therapy has been excessive and/or has extended into this period)

changes—which cause high temperatures and precipitation—contribute to the unprecedented global spread of DF and its associated deaths.

It is important to note that DF transmission follows a cyclical pattern, resulting in significant outbreaks every 3 to 4 years. Understanding this pattern is critical to implement effective prevention and control strategies to protect public health. Nowadays, DF incidence is on the rise in Brazil. In 2023, there were 788.8 cases per 100 thousand inhabitants, a 15.8% increase from the previous year. In total, 1,601,848 probable cases were reported, with 1,053 deaths. Additionally, there was a 17.8% increase in severe DF cases during the same period.[8]

Dengue fever is a systemic disease with a broad clinical spectrum, including severe and non-severe clinical manifestations.[9] Following an incubation period ranging from 3 to 15 days, the illness presents itself abruptly and is characterized by 3 distinct stages: febrile, critical, and recovery. The acute febrile stage usually lasts 2 to 7 days and is often accompanied by facial flushing, skin erythema, body aches, myalgia, arthralgia, and headaches.[9] During the early febrile phase, distinguishing DF from other febrile disorders can be challenging. Furthermore, these clinical signs do not enable the differentiation between severe and non-severe DF cases. As a result, monitoring for warning signs and other clinical features is vital to identify progression to the critical stage. After 3 to 7 days of illness, there may be an increase in capillary permeability and a rise in hematocrit levels.[10] This is the start of the critical stage, which typically lasts between 24 to 48 hours and involves significant plasma leakage. Progressive leukopenia is typically followed by a rapid decrease in platelet count, which can lead to plasma leakage. Shock occurs when a critical volume of plasma is lost through leakage,[11] and the body temperature may drop below normal. If the shock persists, the ensuing organ hypoperfusion causes progressive organ damage, metabolic acidosis, and disseminated intravascular coagulation. In the 48 to 72 hours that follow, extravascular compartment fluid is gradually reabsorbed if the patient makes it through the critical 24-to-48-hour stage. ►**Table 2** summarizes the major clinical problems that arise during the different stages of DF.

PATHOGENESIS

As previously stated, there are four DENV serotypes (DENV1 through DENV4), and all can cause DF and neurological complications.[3] During epidemics, it is possible for more than one serotype to be circulating, and immunity is specific to each serotype. It is imperative to note that individuals who have previously been infected by the DENV are at a higher risk of contracting the disease again if exposed to a new serotype. This is due to the phenomenon of antibody-dependent enhancement (ADE) and should not be overlooked. it occurs when non-neutralizing antibodies bind to the DENV, increasing the ability to invade mononuclear phagocytes, resulting in more rapid viral replication and, potentially, more severe clinical symptoms,[3,12] including neurological disease.

Neuropathogenesis demonstrates how systemic infection-related metabolic abnormalities, autoimmune symptoms, and direct viral infection interact. There is strong evidence that the DENV affects the nervous system, even though it is not considered a neurotropic virus.[13] Viral invasion of the blood-brain barrier (BBB) has been shown in experimental models,[14] and the virus has been detected in the cerebrospinal fluid (CSF).[15] It is believed that non-structural 1 (NS1) antigen, a secreted viral protein cofactor for RNA replication, triggers cytokine release, resulting in BBB damage and endothelial dysfunction.[3] Other probable factors include tumor necrosis factor alpha (TNF-α), leukotrienes, and platelet-activating factor (PAF).[12]

CENTRAL NERVOUS SYSTEM NEUROLOGICAL COMPLICATIONS

Acute meningitis

Headache is a common symptom of DF. However, patients may experience a full meningeal syndrome, with fever, headache, vomiting, and nuchal rigidity.[16] The DENV has accounted for 10% of the cases of acute viral meningitis in an endemic area[17], and Sahu et al.[18] found 7 cases of meningitis out of 484 patients with DF. Meningeal contrast enhancement may be observed in imaging studies.[3]

Encephalopathy

Encephalopathy is the most frequent CNS complication in DF patients.[3,19] It is defined by a decreased level of consciousness associated or not with seizures and behavioral disturbances.[16] Among 2,441 patients with dengue hemorrhagic fever (DHF) in Thailand, it was present in 6%. In Vietnam, a study[3] found a 0.5% incidence among 5,400 patients with serologically-confirmed DHF.[20] It was formerly believed to be exclusively linked to DHF.[16] Encephalopathy could result from various mechanisms, including cerebral anoxia, hyponatremia, metabolic acidosis, liver and renal failure, and the release of toxic substances.[3,16,21] Patients with encephalopathy may present normal CSF parameters, while brain magnetic resonance imaging (MRI) scans could reveal diffuse cerebral edema. Common electroencephalogram (EEG) patterns include diffuse slowing, burst suppression, and focal discharges.[3,22] The outcome is variable and depends on the precipitating factors and the quality of the supportive care.[3]

Encephalitis

Dengue is a frequent etiology of encephalitis in regions where the disease is endemic,[17] and it has been described in all age groups. It is the consequence of the DENV invasion and its neurotropic effects.[21] According to Soares et al.,[17] the incidence of encephalitis was of 47% among DF cases identified in Brazil, and only 50% of them presented systemic DF symptoms. Sahu et al.[18] confirmed that out of 486 people with DENV infection, 33 (6.7%) were diagnosed with encephalitis. The same study found that liver dysfunction, low platelet count, higher hematocrit, and high mean body temperature predicted CNS involvement. When altered consciousness, seizures, focal neurological symptoms, headaches, and behavioral changes are present, together with positive DENV polymerase chain reaction (PCR), NS1 antigen, or immunoglobulin M (IgM) antibody tests in the CSF, and other possible causes of encephalopathy or encephalitis have been ruled out, a diagnosis can be established.[3,12,21,23] The CSF may show pleocytosis, but normal parameters do not exclude the diagnosis.[17] A normal brain MRI scan does not exclude the diagnosis of DF encephalitis.

Several reports of parkinsonism have been associated with or following DENV infection. Typical signs of parkinsonism (rigidity, bradykinesia, tremor, abnormal gait, postural abnormalities) can occur in pediatric or adult patients and are more common in men.[24] Self-limiting cerebellitis has been rarely described.[24]

A variety of patients present imaging abnormalities, and no single finding can be deemed definitive in establishing the diagnosis. Areas of the globus pallidum, thalami, cerebellum, temporal lobes, hippocampus, and brainstem may exhibit increased signal intensity on MRI scans. Microhemorrhages may be evident on susceptibility-weighted imaging (SWI), and diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) sequences may occasionally exhibit restricted diffusion.[3] The "double-doughnut" sign has been documented by multiple authors[25–27] in DF encephalitis; it is characterized by a symmetrical T2-weighted/fluid-attenuated inversion recovery (FLAIR) high signal intensity area in both thalami, restricted diffusion on DWI/ADC, and blooming in the middle region of the gradient echo sequence as a result of hemorrhagic residues. Reversible splenial lesions have also been described.[28] Most patients have a favorable prognosis,[16] although deaths have been described.[18]

Stroke

Both ischemic and hemorrhagic strokes can occur during and after DF. Out of 1,148 patients admitted to the hospital in India with DF, 0.26% had a stroke,[29] while the incidence of hemorrhagic stroke was of 0.06% in the Brazilian population according to a study.[3] A recent study conducted in Taiwan,[30] which involved 13,787 patients, found that the incidence of stroke was higher in the DF cohort (5.33 per one thousand person-years) than in the control group (3.72 per one thousand person-years). The hazard ratio was of 1.16, and the researchers[30] observed the highest risk of stroke within the first two months after the infection. Another recent study found an increased risk in the early postinfection period and patients $>$ 65 years of age.[31]

Hemorrhagic encephalic lesions typically develop a week after the onset of fever,[32] and they may occur in patients who do not experience bleeding at other sites[21] or thrombocytopenia.[3] Bleeding may be caused by endothelial damage leading to increased vascular permeability and plasma leakage[16] or platelet dysfunction and coagulopathy.[3] The most common presentations include hemorrhages in the basal ganglia or lobes, bleeding in the pontine and cerebellar regions, subdural hematoma, non-aneurysmal subarachnoid hemorrhage, and pituitary apoplexy.[3,21]

Ischemic lesions are rare, and watershed infarcts are secondary to systemic hypotension. Small cortical, putaminal, and corona radiata lesions have been described.[30,33,34]

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is typically associated with eclampsia, renal failure, and the use of drugs such as tacrolimus and cyclosporine. Still, there have been rare instances of its association with DF.[35–38] The classic findings include cortical visual loss, seizures, confusion, and decreased consciousness.[3] Vascular damage during acute infection is implicated in the pathogenesis.[36] The typical MRI findings are bilateral and symmetric periventricular and subcortical T2-weighted and FLAIR high signal changes that resolve over weeks.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an autoimmune process that occurs concomitantly or following an acute infection or vaccination. Kamel et al.[39] estimated a 0.4% prevalence of ADEM in DF cases; neurological symptoms, including altered consciousness (58%), seizures (35%), visual complaints (31%), dysarthria (23%), walking disturbances (15%), and ataxia (12%), started between 3-19 days after the onset of DF symptoms, and elevated protein levels were the most common finding in the CSF. Additionally, multiple abnormalities were observed in the deep brain white matter, thalami, brainstem, cerebellum, and spinal cord on both FLAIR and T2-weighted images;[40] in most cases, there was either partial or complete recovery.[39]

Transverse myelitis

Spinal cord lesions following DF are rare.[41] However, a recent study[42] reported transverse myelitis (TM) in 2.3% out of 2,672 cases, while Sahu et al.[18] described myelitis in 7 out of 486 patients (1.4%). The mean time from the onset of DF to TM was of 11.7 days, and this complication was more frequent in men.[42] Spinal cord signal changes and contrast enhancement, including longitudinally-extensive lesions, can be observed.[43,44] Cases with a positive Aquaporin-4 antibody have been reported.[45,46] Half of patients make a full recovery, although the prognosis can vary.[42]

NEUROMUSCULAR INVOLVEMENT

The acute phase of DF often includes severe myalgias and arthralgias ("breakbone fever"). These symptoms are part of

DF's clinical picture and do not always indicate a neurological complication.[1]

Acute inflammatory polyneuropathies (AIPs) and other peripheral nervous system complications

Many acute inflammatory polyneuropathy (AIP) variations have been reported,[12,18,47–59] most commonly after DF; however, there are also sporadic instances of AIP manifesting during the acute febrile stage of DF. The AIPs can be divided into two subtypes: demyelinating and axonal, with varying appearances. The most common demyelinating types are Guillain-Barré syndrome (GBS) and Miller-Fisher syndrome, which causes ataxia, ophthalmoplegia, and areflexia. Guillain-Barré syndrome is the most prevalent cause of acute flaccid paralysis, with symptoms including abrupt, progressive, bilateral flaccid weakness and sensory abnormalities. It is frequently associated with albumin-cytologic dissociation in the CSF examination. The main axonal variants of AIP include acute motor axonal neuropathy (AMAN), which may be clinically indistinguishable from acute flaccid myelitis (AFM), as both typically present with flaccid weakness, areflexia and preserved sensation, and acute motor and sensory axonal neuropathy (AMSAN), which has a presentation similar to that of GBS.[1] There is a reported period of 5 to 15 days between the onset of DENV infection and GBS.[60] A total of 20% out of 97 patients with GBS in an extensive series of DENV-associated GBS had recent DENV infection, as indicated by the positive serum DENV IgM test. Diarrhea, facial palsies, and a more severe illness with a lower Medical Research Council (MRC) sum score, a higher score on the GBS disability scale at nadir, and a need for ventilation were more common in these patients.[48] Extensive demyelination was the most common electrodiagnostic feature in these GBS patients,[48] although Fragoso et al.[60] found AMSAN in all ten patients in their study. Due to the molecular similarities between the DENV polyprotein and GBS-related human proteins, DENV-associated GBS most likely operates by a mechanism similar to that of GBS due to other causes.[61]

When GBS is linked to DENV infection, CSF analysis usually shows an increased protein level with a normal cell count (albuminocytologic dissociation). Regardless of its correlation with DENV infection, this finding is consistent with the classic presentation of GBS. Accordingly, particular CSF results in GBS linked to DENV infection might not be substantially different from those in GBS due to other causes.[41] The treatment of GBS associated with DF is the same as the one for GBS due to other causes, with no difference in prognosis.[19]

Cranial neuropathies are rare manifestations of acute DF, and the most affected cranial nerves are the 7th, 2nd, 6th, and 3rd.[62–67] In some studies,[18,41,68] brachial neuritis (neuralgic amyotrophy), resulting from a presumably immune-mediated mechanism, has also been reported with DF. Finally, rare cases of mononeuritis multiplex and mononeuropathy,[63] radiculitis,[69] and isolated and self-limiting phrenic neuropathy with diaphragmatic palsy have also been reported.[70]

Myopathy, rhabdomyolysis, and hypokalemic paralysis

While myalgia is a common symptom of DF, true myositis and muscle weakness are relatively rare.[1] In most cases, the benign and self-limiting nature of the disorder has led to the proposal of the term "dengue-associated transient muscle dysfunction".[20] However, several case series and case reports[1,71–82] describe a true DF-related inflammatory myopathy.

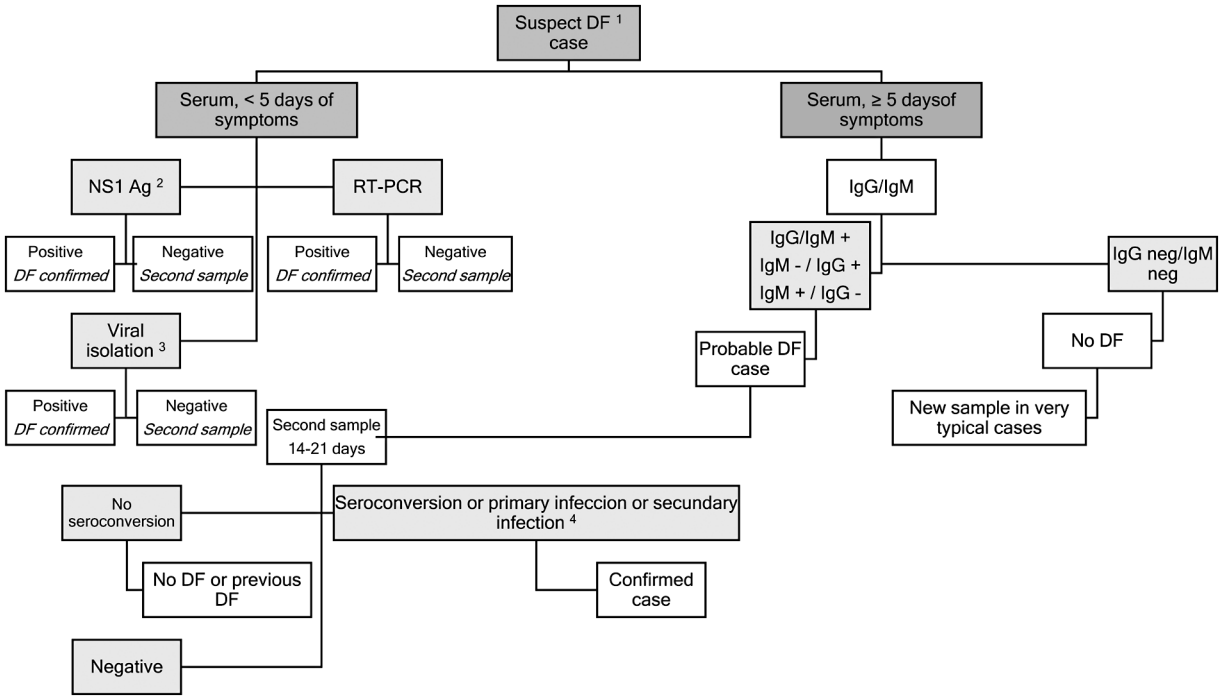
The diagnosis of DF myositis diagnosis is based on clinical manifestations of DENV infection, positive serum IgM for the DENV, high creatine phosphokinase levels, normal CSF, and exclusion of other causes.[77] The symptoms are broad, ranging from moderate asymmetrical weakness in the lower limbs to abrupt, severe trunk and limb weakness, and even respiratory failure. Dengue myositis is considered a relatively benign and self-limiting disease in pediatric reports;[16] however, in adult patients, it is often more severe, even leading to severe rhabdomyolysis.[83] Severe myalgia, early respiratory muscle involvement, and very high creatine phosphokinase (CPK) levels suggest a form of DF myositis with a poor prognosis.[77] Electromyography (EMG) usually shows normal motor unit potentials of reduced duration and amplitude and polyphasy. Fibrillations, sharp waves, and complex repetitive discharges do not occur.[16,76]

The physiopathology of DF myositis is still unknown. The two suggested mechanisms are DENV direct invasion of muscles or an immune-related muscle fiber destruction mediated by the TNF.[74] Pathologically, DF myositis is characterized by perivascular infiltration of mononuclear cells, mitochondrial proliferation, fat accumulation, nuclear centralization, fiber-type grouping, and/or myonecrosis foci on muscle biopsy.[74,76]

Dengue-related rhabdomyolysis[84,85] occurs when the DENV triggers the release of cytokines, specifically TNF and interferon alpha, which destroy muscle cells. The increased levels of cytokines raise the amount of free calcium in the cells, which can damage muscle cells by activating proteases. This process also creates mitochondria dysfunction and generates too many reactive oxygen species, ultimately leading to the death of muscle cells. Additionally, rhabdomyolysis can cause severe electrolyte abnormalities and acute kidney injury (AKI).[12,76]

Hypokalemic paralysis has been reported in various case studies and series associated with DF.[1,3,12,16,18,41,86–88] The patients report abrupt onset of limb paralysis without involvement of the cranial nerves, bladder, or bowel functions. The onset of weakness often occurs between the second and fifth days of fever, lasting 4 to 24 hours. Muscle stretch reflexes are usually absent or decreased[58] in most patients. A blood potassium level of 3 mmol/liter or lower is frequently used to indicate hypokalemia-induced paralysis. The pathogenesis of hypokalemia in DF is not clear. Several mechanisms have been proposed:

- Excess intravenous fluid, especially lactate-containing solutions, may cause metabolic alkalosis, which lowers serum potassium by shifting potassium intracellularly



Notes: [1]Dengue fever; [2]NS1 antigen has a sensibility of 34 to 76% with 100% of specificity; [3]viral isolation is rarely used in the clinical practice; [4]seroconversion: a negative immunoglobulin M (IgM) sample that becomes positive in the second sample or an immunoglobulin G (IgG) sample that quadruples its value titers in the second sample with respect to the value of the first sample.
Figure 2 Proposed algorithm for the laboratory diagnosis of dengue fever.

- Systemic infection redistributes potassium within the cells and extracellular fluid
- Temporary renal tubular abnormalities enhance potassium excretion; and
- Catecholamine release from stress causes cellular potassium absorption and hypokalemia.

Dengue-associated hypokalemic paralysis can also be caused by a virus-induced channelopathy.[3] Patients with DENV-associated hypokalemic paralysis recover quickly with minimal potassium supplementation, without impairments.[3]

DIAGNOSIS

Dengue has a broad differential diagnosis. Other viral infections (such as measles, rubella, enterovirus, adenovirus, influenza, and other arboviruses), bacterial infections (such as leptospirosis, Rickettsia and typhoid fever), and parasite infections (such as malaria) that may exist in DF endemic areas share similar features.[89,90] Consequently, DF can be challenging to diagnose clinically based on factors such as the patient's infection stage and geographic location. Early laboratory detection of DENV might be lifesaving, since certain patients can rapidly progress from mild disease to severe conditions and even death.[89]

Serological and molecular tests are used in the laboratory diagnosis of DF;[91] the molecular test is based on detecting and amplifying the viral genome. The techniques for virus isolation and culture, which are very labor-intensive and not easily accessible, are rarely employed in the clinical practice. Whether the patient is in the acute or convalescent stages of the disease will determine which tests are appropriate.[90] An algorithm for DF diagnosis is shown in ►**Figure 2**.

Acute stage

The first seven days following the onset of symptoms is known as the acute stage of DF. The DENV is commonly found in blood or blood-derived substances such as serum or plasma during this time. Molecular techniques can be used to detect DENV RNA. Commercial assays can also identify the DENV protein known as non-structural protein NS1. A molecular or NS1 test result that is negative is not definitive. Any serum sample from individuals exhibiting symptoms within the first seven days of their illness should be examined using an IgM antibody, real-time PCR (RT-PCR), or the NS1 test. During this time, both molecular and IgM antibody (or NS1 and IgM antibody) testing can identify more cases than performing a single test, and most of the time, a single sample can be used for diagnosis.

Convalescent stage

The seven-day interval that follows the onset of symptoms is referred to as the convalescent stage of DF. Patients with negative IgM antibody and nucleic acid amplification test (NAAT) or negative NS1 test results within the first week of the illness should have a convalescent sample analyzed for IgM antibodies. These antibodies are typically present during the convalescent stage and can be reliably identified using an IgM antibody test. Dengue IgM antibodies may remain detectable for at least three months following infection. Patients are classified as having a presumptive, recent

DENV infection if an IgM antibody test detects IgM antibodies against DENV in their serum specimen and if the acute-stage specimen does not contain a negative NAAT or NS1 result, or there is no acute-stage specimen available.

In summary, to diagnose DF in the acute stage, the preferred tests are IgM antibodies, RT-PCR, or NS1 antigen. The IgM antibodies appear from the fifth to the eighth days, RT-PCR is positive until the seventh day, and NS1 antigen is positive until the seventh day. During convalescence, IgM antibodies can still be present up to 90 days after the illness. A positive IgG antibody test alone cannot confirm a recent infection, as it may indicate a previous infection.[91]

One of the limitations of DF serologic assays is cross-reactivity. The DENVs can cross-react with other flaviviruses, including the zika, West Nile, Japanese encephalitis, and St. Louis encephalitis viruses,[91] and patients who reside in or have been to places where other flaviviruses co-circulate need to consider this constraint. Therefore, when testing for IgM antibodies against the DENV, a patient with other recent or past flavivirus infection(s) may test positive. To more precisely determine the cause of the disease in IgM-positive patients, the IgM-positive specimens can be tested for specific neutralizing antibodies through the plaque reduction neutralization test (PRNT; against the four DENV serotypes and other flaviviruses); however, the PRNT does not always conclusively distinguish specific flaviviruses.[91] Clinicians may discuss with state or local public health laboratories about the appropriate tests that are available to distinguish the DENV from other flaviviruses for individuals who live in or are visiting an area where the DENV, zika, and other flaviviruses are endemic or concurrently circulating. Considering the unique characteristics of the Brazilian population, the Brazilian Ministry of Health provides a handbook with instructions for the diagnosis and treatment of DF, which is accessible and can be downloaded on its website.[8]

A current DF diagnosis is confirmed if a NAAT or NS1 test is positive for DENV infection. If the NAAT result is negative and the IgM antibody test is positive, the laboratory diagnosis is presumptive DENV infection.[91]

Although virus isolation, RT-PCR, hemagglutination inhibition, and enzyme-linked immunosorbent assay (ELISA) for the detection of the DF non-structural antigen-1 (NS1) or DF-specific immunoglobulin (IgM/IgG) can confirm the diagnosis, they are resource-intensive and not suitable for many low-resource settings. The growing demand for point-of-care diagnostics gave rise to many rapid DF diagnostic tests that flooded the market in the past two decades and have been extensively studied in more recent years.[92]

Like the serum, the CSF can be subjected to viral culture, and viral nucleic acid or DENV antigen assay can be performed early, in 5 to 7 days. After that, the IgM or IgG serological assays are helpful. Isolation of the virus from culture, viral nucleic acid positivity, antigen positivity, or IgM positivity in the CSF for DENV suggests encephalitis rather than just encephalopathy. The CSF analysis can also show lymphocytic pleocytosis and/or elevated protein. Patients with malaria, leptospirosis, and past DENV infection may sometimes present false-positive results, and cross-reactivity with other flaviviruses, such as that of yellow fever, can also yield false-positive results.[41] The DENV can be identified in the CSF by PCR.[93]

Potassium measurements, EMG, and CPK levels should be requested in cases suspected of hypokalemic paralysis or DF-associated myositis to confirm the clinical diagnosis.

GENERAL TREATMENT

Currently, there are no definite effective antiviral agents available to treat DENV infection.[94] The general supportive therapy includes intensive hematological monitoring, fluid replacement, and blood transfusions as needed. Nonsteroidal anti-inflammatory drugs can worsen gastritis and cause bleeding; therefore, they should be avoided.[4]

Numerous studies on specific and nonspecific antivirals against DENV have been conducted, but only a few have progressed to the clinical trial stage. Most failed to reduce viremia, improve cytokine profiles, or shorten fever duration. More recently, a phase-1 clinical trial revealed that a novel pan-serotype NS3-NS4B inhibitor (JNJ-1802) was safe and well tolerated; it is undergoing a phase-2 trial to ascertain its efficacy in humans.[95]

NEUROLOGICAL TREATMENT

There is no particular treatment for any of the neurologic complications of DF, like encephalitis or encephalopathy. However, supportive care and symptomatic treatment are essential, such as steroids for myositis, myelitis, and encephalomyelitis, mannitol or diuretics for elevated intracranial pressure, and antiepileptics for seizures. According to published research, immunomodulators effectively treat GBS cases caused by DENV infection (intravenous immunoglobulin therapy). Potassium supplementation results in full recovery from hypokalemic paralysis.[41]

Although neurotoxicity has not been reported in licensed DF vaccines, the potential neurological consequences after more widespread use are unknown. Therefore, it is essential to continue monitoring the long-term effects of these vaccines to ensure they remain safe for use and protect public health.

PREVENTION

To prevent DF epidemics, a combination of strategies is needed to reduce the population of mosquitoes that transmit the virus and minimize human-mosquito contact. Some effective measures include mosquito control, personal protection, community engagement, public campaigns, vector surveillance and management, health system strengthening, and investing in research for new vector-control methods, vaccines, and treatment options for DF. By implementing these preventive measures comprehensively and consistently, communities can reduce the risk of DF epidemics and protect public health.

Several DENV vaccines are currently being developed and tested in clinical trials.[19,90,96] The two presently-licensed

DENV vaccines are Dengvaxia (Sanofi Pasteur, Lyon, France) and Qdenga (TAK-003, Takeda Pharmaceuticals, Tokio, Japan). The primary goal of DENV vaccine development is to generate neutralizing antibodies against each of the four DENV serotypes. This is done in order to stop the development of non-protective, cross-reactive sub-neutralizing antibodies that could lead to antibody-dependent enhancement in response to a subsequent DENV infection. In addition, regardless of DENV immune status, the optimal vaccination should protect against all serotypes and phenotypes, from mild to severe, in all age groups. But even with strong neutralizing antibody titers to all serotypes in phase-3 trials, Dengvaxia appears to provide superior protection against DENV4, and Qdenga appears to provide better protection against DENV2.[96] Dengue vaccines are also being evaluated using the same successful mRNA vaccine technique used for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which could yield new DF vaccine candidates.[96]

Dengvaxia is a live, attenuated, recombinant, tetravalent DF vaccine that is the first vaccine approved for the prevention of symptomatic DF in individuals aged 9 to 60 years by any of the 4 DENV serotypes in many endemic areas. The decreased effectiveness of the Dengvaxia vaccine against DENV2, a notably severe strain associated with DF outbreaks, raises significant concerns about its ability to provide adequate protection. The risk of severe DF is recognized to be greater during a secondary infection compared to a primary infection. Thus, there is a theoretical proposition that administering Dengvaxia to an individual without previous DENV exposure may mimic a primary infection and increase the risk of developing severe DF during a subsequent natural infection after immunization. Clinical research has revealed anti-DENV antibodies that remained after five years without posing any health risks. In individuals previously exposed to DF, a 3-dose regimen at intervals of 0, 6, and 12 months was recommended. Dengvaxia is currently licensed and accessible for use by people aged 9 to 45 in 20 different countries. The WHO advises administering Dengvaxia exclusively to individuals who have a history of confirmed DENV infections. By taking this calculated risk, the possibility of severe DF is reduced in the unlikely event that these people contract the virus after being vaccinated. This concern was addressed after an analysis of the data from three efficacy trials, which demonstrated that this vaccine protects seropositive individuals against DF and DF-related hospitalization for five years. However, there is evidence that individuals who are not exposed to the DENV have a higher risk of developing DF, potentially heightening the susceptibility to severe DF following a subsequent natural infection postvaccination.[97]

The Qdenga vaccine showed significant protection against symptomatic DF over a period of three years. It was found to be effective against symptomatic DF in a clinical trial including children in eight countries where DF is common, which was conducted over a period of three years. The effectiveness may decrease over time; however, its strength remained unchanged in hospitalized DF cases. The DENV2 exhibits a high level of neutralizing antibodies compared to serotypes 1, 3, and 4, which present lower responses. Qdenga demonstrates long-term effectiveness in treating DF in hospitalized patients without raising the risk of hospitalization or significant safety concerns. It is efficacious and well-tolerated in individuals who are both DENV-naive and DENV-exposed. Seroconversion occurs for all forms of DENV. A rash is a typical side effect that affects the entire body and is linked to a fourfold immunological reaction.[97]

Instituto Butantan, in the city of São Paulo, Brazil, the United States National Institutes of Health (NIH), and Merck & Co., Inc. are conducting a phase-3 trial for Butantan-DV, a vaccine similar to the NIH's TV-003 (Merck & Co., Inc., Rahway, NJ, United States). The efficacy data available after two years revealed that the overall efficacy against DENV1 was of 89.5% and of 69.6% against DENV2, with higher efficacy among seropositive individuals than seronegative individuals.[19,90,96]

In December 2023, Brazil became the first country to offer a DF vaccine through its Unified Health System (Sistema Único de Saúde, SUS, in Portuguese). The vaccine provided in Brazil is the Qdenga, which is indicated for anyone aged 4 to 60 years without a history of DENV infection. The vaccine has been administered to individuals living in endemic areas in 521 municipalities. The selection of these regions was based on criteria such as high transmission rates throughout the past decade and the prevalence of the DENV2 serotype. The target audience is children and adolescents aged 10 to 14 years, who present the second highest rate of hospitalization for DF, only behind elderly individuals, who are not authorized to receive the vaccine yet. The immunization schedule comprises two doses administered three months apart and includes four distinct serotypes of the DENV. Vaccination began in February 2024.[98]

Authors' Contributions

All authors have contributed equally to the manuscript's conceptualization, design, data acquisition, analysis, interpretation, writing, and reviewing. All authors have approved the final version of the manuscript and agreed to be responsible for all aspects of the work.

Conflict of Interest

The authors have no conflict of interest to declare.

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