Curr Neurol Neurosci Rep (2015) 15: 29
DOI 10.1007/s11910-015-0550-4

INFECTION (ML SOLBRIG, SECTION EDITOR)

Current Neurological Observations and Complications of Dengue Virus Infection

Marylou V. Solbrig[1] · **Guey-Chuen Perng**[2]

Published online: 17 April 2015

Abstract Dengue, a mosquito-borne flavivirus and fastest growing tropical disease in the world, has experienced an explosion of neurologic case reports and series in recent years. Now dengue is a frequent or leading cause of encephalitis in some endemic regions, is estimated to infect one in six tourists returning from the tropics, and has been proven to have local transmission within the continental USA. High documentation of neurologic disease in recent years reflects increases in overall cases, enhanced clinical awareness and advances in diagnostics. Neurological aspects of dengue virus, along with epidemiology, treatment, and vaccine progress, are presented.

Keywords Encephalitis · Encephalopathy · Flavivirus · Viral hemorrhagic fever · Vaccine

Introduction

Encephalitis is a reportable disease in many countries and jurisdictions. Its medical presentation is sufficiently severe to be a good marker for emergence of a new pathogen in a new geographic area. Examples such as West Nile, polio and other enteroviruses, LaCrosse, Japanese encephalitis, equine encephalitis viruses, are familiar. Several years ago, dengue would not have been considered in the same way, as a sentinel encephalitis virus. However, dengue encephalitis is now accepted as a clinical entity. Dengue is recognized as a frequent or leading cause of encephalitis in endemic regions [1, 2••, 3••, 4, 5], and dengue encephalitis may be the primary manifestation of infection [6].

Previous WHO guidelines for classification of symptomatic dengue infections such as dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have been used for several decades and has supported decision-making for the management of dengue [7, 8]. This classification is very specific but the sensitivity has been considered to be low. As such, now they have been revised to include severe organ manifestations, to capture severe cases that need ICU treatment, and severe organ manifestations now include the CNS. The new dengue case classification, modified by WHO in 2009, classifies the disease as dengue without warning signs, dengue with warning signs, and severe dengue, with one definition for severe dengue as involvement of the CNS with impaired consciousness [9]. Specific neurologic complications are not well described in the 2009 guidelines, although to date there have been more than 200 published reports, case series, and studies of neurological, neuromuscular, and neuro-ophthalmologic complications of dengue. The high sensitivity and low specificity of the 2009 guidelines is being addressed by newer comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever, such as the revised and expanded edition implemented by SEARO WHO Regional Office in 2011.

The number and variety of dengue-associated neurologic syndromes in what was historically not an encephalitic virus is interesting and will prove important for advancing our

This article is part of the Topical Collection on *Infection*

✉ Marylou V. Solbrig
msolbrig3@ku.edu

Guey-Chuen Perng
gperng@mail.ncku.edu.tw

[1] Department of Pharmacology and Toxicology, School of Pharmacy, University of Kansas, 1251 Wescoe Hall Drive, Malott Hall Rm 5040, Lawrence, KS 66045, USA

[2] Department of Microbiology and Immunology, College of Medicine, and Center of Infectious Diseases and Signaling Research, National Cheng Kung University, #1 University Rd, Tainan 70101, Taiwan

knowledge of viral causes and contributions to CNS disease. For example, a syndromic approach to viral pathogenesis, with full characterization of patients, risk factors, and virus, has the potential to advance our understanding of fundamental medical virology: who gets sick and who does not. Moreover, better comprehension of all aspects of the disease is an urgent need, given that an estimated 390 million persons worldwide are infected annually with dengue [10•], there is no licensed prophylactic vaccine and no specific antiviral drugs.

General/Clinical

Dengue fever, a syndrome of febrile myalgias, arthralgias, frontal and retroorbital headache, abdominal pain, nausea, vomiting, rash, results from infection with one or four closely related dengue virus serotypes (DENV1-4) that circulate simultaneously in endemic areas. Dengue viruses are single-stranded RNA viruses of the Flaviviridae family. Transmission is by the day-feeding African mosquito *Stegomyia* (formerly *Aedes*) *aegypti* and the Asian Tiger mosquito *Stegomyia* (formerly *Aedes*) *albopictus* [11]. More than one third of the world's population, or 4 billion people are at risk for infection, and there are an estimated 390 million infections and nearly 100 million people with symptomatic dengue each year [10•]. Increasing globalization, rapid human movement, and unplanned urbanization coupled by the increase in the geographic area that the *St. aegypti* mosquito vector inhabits have supported the spread of dengue virus infection to nearly every corner of the world, almost all tropical and subtropical countries. The highest incidences of dengue are in Asia, Central and South America, and sub-Saharan Africa.

St. aegypti, the more efficient vector for DENV, is present in limited areas of the southern USA while *St. albopictus* is more widely distributed. In the USA, since 2001, three autochthonous dengue fever outbreaks have occurred: Hawaii (2001), Brownsville, Texas (2005), and South Florida (2009–2011). Twenty-six dengue cases were acquired in Key West, Florida, in 2009 and 63 cases in 2010. Transmission was confirmed by detection of DENV1 in local mosquitoes and *Aedes aegypti* mosquito pools [12•, 13, 14]. In 2012, as of December 11, 2012, there had been 3937 locally acquired dengue fever cases in the USA: four in Florida and 3933 in Puerto Rico, where dengue is considered endemic (source, CDC). Retrospective laboratory testing of hospitalized meningitis and encephalitis patients raised the possibility of an additional dengue outbreak in Houston in 2003 [15, 16]. Today, one in six tourists returning from the tropics are estimated to be infected with dengue. Incubation period is 3 to 14 days.

Severe dengue is most consistently in the late acute or early convalescent phase of secondary dengue infections and severe complications are associated with high DENV titers. Dengue hemorrhagic fever in Asia is generally a disease of childhood. In infants, the disease is associated with primary infection and the presence of maternal antibody from a different strain. Most cases in older children are due to secondary or a sequence of multiple serotype infections [17, 18]. However, there is some evidence that the incidence of severe dengue disease may be occurring at similar rates between primary and secondary dengue virus infection in the adult population [19], and in non-endemic regions (Taiwan), that naïve adult populations are the most likely to develop severe dengue [20].

DHF is defined by the presence of fever, hemorrhagic features, thrombocytopenia, and evidence of plasma leakage. DSS has increased vascular permeability, plasma leakage, circulatory failure, hypotension, and shock. Factors associated with DSS are the following: bleeding signs, plasma leakage signs, thrombocytopenia, coagulopathy, hepatic disease, digestive factors, female gender, malnutrition, and increased age of child [21]. Encephalopathy is strongly associated with DSS, due to shock, electrolyte imbalance, liver failure, systemic inflammation, and/or direct organ invasion. Although CNS involvement in this setting would be thought an encephalopathy secondary to capillary leakage, reports show increasing prevalence of dengue encephalitis in dengue-prone regions [22]. A recent study of fatal dengue cases demonstrated DENV in 48.8 % of CSF analyzed by RT-PCR, NS1Ag, or IgM detection [2••]. Mechanisms of CNS injury and direct viral effect are incompletely understood, due in part to dynamic aspects of disease (rapid changes in quantifiable pathophysiological parameters) and in part to the differences in behavior between serotypes. For example, viral load in DF and DHF is significantly different (Fig. 1a), and days of sample collection appear critical in the measurement of serum viral load (Fig. 1b). While each individual dengue viral serotype can induce both DF and DHF, viral load is similar in infections caused by serotypes 1, 2 and 3, with higher viral load observed in DENV1, DENV2, and DENV3, compared with that of DENV4 (Fig. 1c). Only the viral load of DENV2 reveals a significant difference between DF and DHF (Fig. 1d). The observation raises the question whether DENV2's association with increased viral load in severe disease contributes to encephalitis more often than other serotypes.

Neurological Dengue

Neurologic manifestations of DENV infection have been recorded in 0.5–20 % of patients admitted to hospitals with classic dengue and 4–47 % of patients admitted with encephalitis-

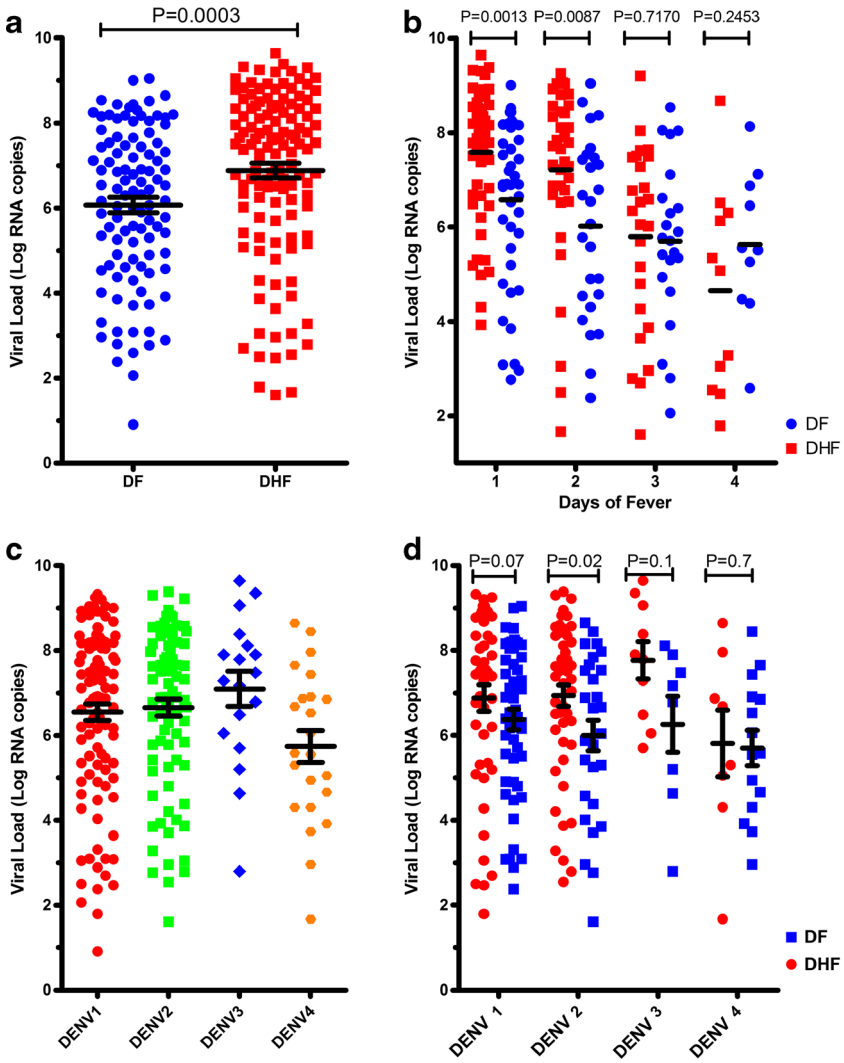

Fig. 1 Dengue viral load in patients. **a** Significantly higher viral load was generally observed in specimens collected from DHF patients compared to that of DF, when first hospitalized, regardless of the day of fever or illness. **b** However, viral load measures depended on day of fever. Time course study showed that dengue viral load in DHF patients was significantly higher than that of DF in the first 2 days of fever, without differences on day 3, and lower on day 4. **c** When grouped by serotype, there were no observable differences or relation between viral load and disease severity within the group. **d** Only DENV2 serotype demonstrated a consistent difference in DHF and DF in viral load, while other serotypes did not show a difference in viral load of DF and DHF

like illness in endemic areas [3••]. Dengue infection results in a wide spectrum of neurologic involvement, from transient muscle dysfunction to encephalitis, overlapping syndromes, and everything in between. The multitude of syndromes reflects one or more of the following pathogenic factors: metabolic disturbances, autoimmune or exaggerated immune reactions, direct viral invasion. The patterns compel expanding investigations into their development and treatment.

The list of CNS and ocular diagnoses reported with dengue, as pure dengue fever or dengue hemorrhagic fever includes meningitis, meningoencephalitis, bitemporal encephalitis, thalamic lesions, cerebellitis, opsoclonus-myoclonus, encephalopathy, subdural hematoma, ischemic or hemorrhagic stroke, intracranial hemorrhage, cerebral vasculitis, myelitis, acute disseminated encephalomyelitis, retinochoroiditis, and retinal vasculopathy. Encephalopathy includes depressed sensitivity, cognitive disorders, convulsions, mood, personality and behavior disorders, as acute mania, emotional lability, depression, anxiety, psychosis, or agoraphobia [23–25]. EEGs can show burst suppression, focal patterns, seizures, or *epilepsia partialis continua* [26–29].

Associated peripheral syndromes are the following: Guillain-Barre, acute motor sensory axonal neuropathy, mononeuritis multiplex, brachial plexitis, hypokalemic quadriparesis or plegia, diaphragmatic paralysis, and myositis [30–35]. Myositis can be severe with intense myalgia, elevated CPK, and early respiratory involvement. Development of hypokalemic paralysis may be a function of potassium loss due to renal tubular acidosis or dysfunction, and/or intracellular shift of potassium from release of catecholamines and insulin accompanying a stress response [30].

Convalescent or post-dengue immune-mediated syndromes include the following: ADEM, transverse myelitis, *neuromyelitis optica*, cranial neuropathies and Miller-Fisher variant GBS, and arteritis [3••, 36••].

Predictors of CNS involvement are higher mean body temperature, elevated hematocrit, low platelet count, and liver

dysfunction, and predictors of PNS involvement are higher mean body temperature, rash, and elevated hematocrit [37]. High APTT, serum IgM, and IgG antibodies also occur in dengue encephalitis.

Neuroimaging

Dengue encephalitis may appear normal or abnormal on MRI [38, 39]. Neuroimaging features of patients with dengue are variable, involving gray and/or white matter, and include signal changes in the thalamus, basal ganglia, hippocampus, internal capsule, and subcortical white matter. Cerebral edema is the most commonly reported, and foci of hemorrhage are possibly more frequent than for other encephalitides. Nonspecific imaging changes have not been correlated with particular hematologic or biochemical findings or specific outcomes [40].

Of note are clinical and MRI overlap with other encephalitides, such as bitemporal lesions with HSV-1 encephalitis [41, 42] and deep gray or thalamic abnormalities seen in other flaviviruses. No pathognomonic imaging features have been designated, but presumed unique MRI findings of bilateral subcortical, thalamic, brainstem, and cerebellar involvement, together with T1 post-contrast "rim-enhancing" lesions of brainstem despite normal CSF have been reported [43].

Diagnosis

Diagnosis of acute dengue is by detection of viral antigens, viral RNA, or dengue-specific antibodies in the blood [as immunoglobulin M IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) and indirect immunoglobulin G ELIS A]. Limitations of the serology tests are cross-reactivity with other flaviviruses, so that a comprehensive pool of antigens is needed, and that dengue antibodies are best detected starting at 5 days into illness. Thus, testing of acute samples for flavivirus IgM can have suboptimal sensitivity and specificity if performed early. Methods for IgM detection 5 to 30–60 days after symptom onset are estimated to have 92 % sensitivity and 99 % sensitivity [36••]. In some cases, IgM is not detected in secondary infection. Commercial methods for NS1 antigen detection in serum have an estimated 52–66 % sensitivity and 90–100 % specificity [36••]. An immunochromagraphic commercial kit for simultaneous detection of IgG, IgM, and NS1 antigen has been developed.

Diagnosis of CNS disease is by demonstration of DENV IgM or viral RNA in CSF, dengue NS1 antigen in CSF, or virus isolation from CSF and exclusion of other causes of viral encephalitis and encephalopathy. Nucleic acid tests as RT-PCR from CSF are estimated to have 93–100 % sensitivity, depending on the serotype and need to be performed during viremia. Early in the course of infection, CSF nucleic acid tests can be positive before IgM and IgG become detectable [36••].

A proportion of cases of dengue with CNS involvement have no CSF pleocytosis and no other organ or systemic complications, such as severe hepatic disease, rendering difficulties classifying these as encephalitis or encephalopathy. Antibody syndromes or metabolic disorders and challenges not screened by routine lab panels may fill in some of the gaps in their categorization.

Metabolism Hypotheses

The kynurenine pathway of tryptophan metabolism, induced by inflammation and stress, is a biochemical pathway linked to inflammatory disorders, cancers, and treatment-resistant depression. The fate of tryptophan is in the comparative activities of enzymes indoleamine 2,3-dioxygenase (IDO)/tryptophan 2,3-dioxygenase (TDO) to produce kyurenine and tryptophan hydroxylase (TPH) to produce serotonin (Fig. 2). An estimated 5–10 % of tryptophan is shuttled through the TPH/5-HT pathway. Although the pathway has remained relatively underrecognized in its implications for systemic and brain disease, dengue patients have been shown to have increased IDO activity, reduced L-tryptophan, increased L-kynurenine in serum during the febrile phase [44].

High kynurenine (KYN) and low 5-HT potentially have a role in pathogenic features of systemic dengue. KYN has been identified as an endothelium-derived relaxing factor directly contributing to hypotension in human sepsis [45, 46] and kynurenine metabolism and metabolites downregulate the immune response [47, 48].

In the brain, KYN and its metabolites can directly and indirectly influence function, giving clinical significance to the accumulation of neuroactive tryptophan metabolites [49]. KYN is able to cross the blood-brain barrier [50]. Elevated

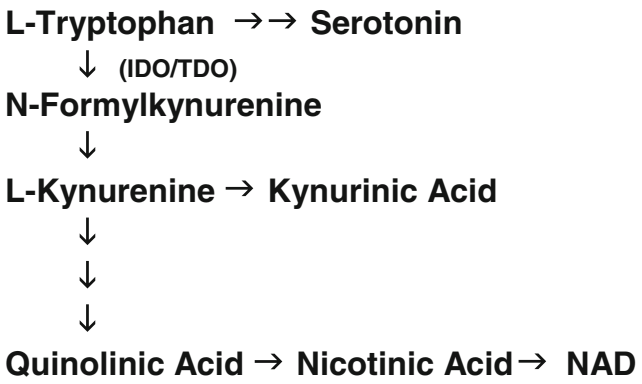

Fig. 2 Tryptophan metabolism. Tryptophan is shuttled through kynurenine or serotonin (5HT) pathways of metabolism, with kynurenine pathway metabolism (as KYN to quinolinic acid) contributing to de novo synthesis of NAD+. *KYN* kynurenine, *QA* quinolinic acid, *KA* kynurenic acid (based on 66)

peripheral KYN, in turn, increasing CSF KYN and its metabolites quinolinic acid (QA) and kynurenic acid (KA) [51] would bind to NMDA receptor sites with agonist and antagonist activity, respectively [52]. QA is well-known as an excitotoxic NMDA receptor agonist, involved in a number of neurodegenerative and convulsive disorders [53]. KA, an NMDA receptor antagonist, could protect against excitotoxins [54]. However, KA also antagonizes the NMDA receptors involved in cognitive functions and has the potential to cause cognitive deterioration [55].

Beyond toxic metabolite production and serotonin biosynthesis, changes in L-tryptophan metabolism also would have consequences for the biosynthesis of NAD+ (nicotinamide adenine dinucleotide) (Fig. 2). KYN pathway dysregulation favoring KA and ultimately lowering of NAD+ production may be a mechanism of virus-induced fatigue, depression, or cognitive slowing. In mammals, nicotinic acid, of nutritional origin, is a precursor of NAD+, and niacin is the 1–3 substituted form. Cognitive and depressive symptoms could signify a pellagra-type syndrome of niacin deficiency and provide a specific example of how better nutritional status associates with better outcomes.

CNS Pathogenesis

The pathogenesis of dengue neurologic disorders and underlying virus and host vulnerability factors are incompletely understood. Monocytes are one of the principal cell types infected by dengue, as monocyte lineage cells are major targets for dengue [56]. Mechanisms of CNS viral entry may be passive transfer through CNS hemorrhage, plasma leakage, or blood-brain barrier injury and infiltration of infected monocytes/macrophages. Specific agents of barrier injury are auto- or self-reacting antibodies, inflammatory cytokines (particularly TNF-alpha and IFN-gamma), histamine release, nitric oxide, apoptotic processes, and complement reactions [57].

The possibility of active CNS virus invasion is supported by detection of viral RNA or antigen in CSF or brain tissue when serum is negative for virus, associated CSF pleocytosis, parenchymal inflammatory cell infiltrates, and intrathecal synthesis of dengue-specific antibodies [2••, 58].

Besides monocytes and macrophages, DENV has been shown to interact with various other cell types, including dendritic cells, hepatocytes, and endothelial cells [59]. Previous studies have suggested DENV enters target cells after the viral envelope protein E attaches to a cell receptor. Multiple cell surface molecules involved in DENV binding and infection in different target cells include GRP (glucose regulated protein) 78, heat shock proteins 70 and 90, LPS-binding CD 14-associated molecule, laminin receptor, mannose receptor, DC-SIGN (these are summarized in [60].

Human neurons in culture are reported permissive for infection and sustain active replication, as shown by demonstration of NS3 viral antigen in primary cultures. Several, as yet unidentified, membrane proteins of gray matter bind the entire virus particle, are thought to act as receptors or co-receptors during CNS infection [57].

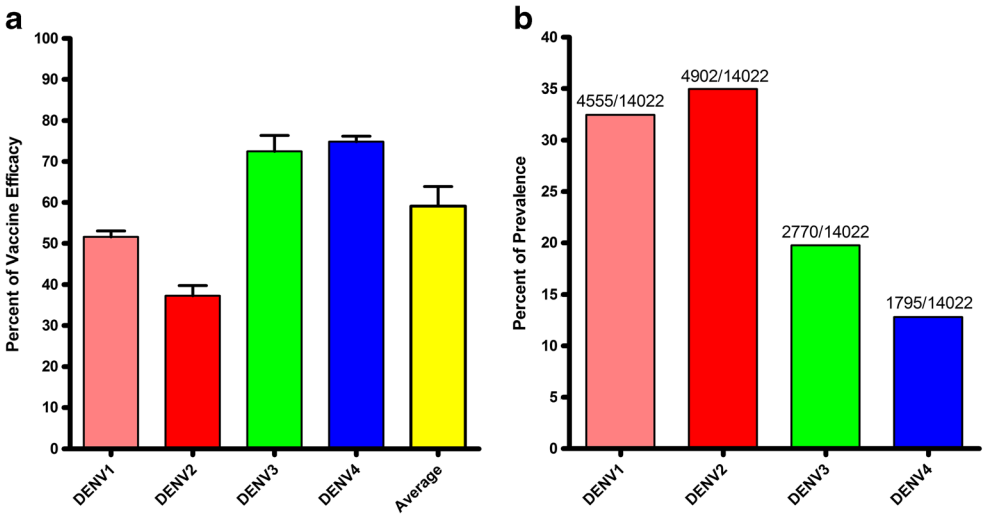

Fig. 3 Comparison of cumulative vaccine data of recent phase III clinical trials in both Asia and Latin America on serotype efficacy, with DENV serotype prevalence during outbreaks in Thailand. **a** Dengue vaccine efficacy to DENV serotypes averaged over recent clinical phase III trials [63••, 64•]. Although overall average efficacy is around 60 %, the efficacies to both DENV1 and DENV2 were at 50 and 35 % respectively, while DENV3 and DENV4 were higher at 70 and 72 %, respectively. **b** Confirmed dengue cases among DENV serotypes over the last 8 years of study from Thailand, by serotype. The prevalence of DENV1 and DENV2 was at 33 and 35 %, respectively, while DENV3 and DENV4 were at 20 and 12 %, respectively. Prevalence data raises the question of whether vaccine efficacy is a function of DENV serotype prevalence alone

Treatment

There are no specific antiviral drugs for dengue. Guidelines for supportive therapy emphasize attention to fluid maintenance and balance. Invasive medical procedures such as nasogastric tube placement, intramuscular injections, and arterial punctures, should be reduced or avoided, along with drugs that increase bleeding risk, such as NSAIDs and acetylsalicylic acid. Complications are managed expectantly or as they occur. Whole blood or packed red cells are given for hemorrhagic complications, rather than platelets or fresh frozen plasma [9]. Convalescent, para- or post-viral neurologic complications needing treatment would be managed by immune therapies appropriate to the syndrome.

Sequelae

Systematic study of long-term neurological sequelae has been limited. Post-infectious fatigue syndrome at 6 months was documented based on telephone interview fatigue questionnaire following a 2005 epidemic in Singapore [61]. Persistent symptoms of physical and mental fatigue, weakness, headache, dizziness, and lost memories were reported 2 years after symptomatic DF or DHF during a 2006 epidemic in Cuba, along with elevated dengue IgG in serum and autoimmune or inflammatory markers in blood in many cases [62].

Prevention

Presently, there is no approved dengue vaccine. Vaccines for dengue have been developing since the 1940s, and now there are six vaccines at various clinical trial stages [63••]. The farthest along is Sanofi's ChimeriVax, a tetravalent vaccine composed of four recombinant, live attenuated viruses (yellow fever 17D/DEN chimeric viruses), which has completed phase III trials in Asia [64•] and Latin America [65•]. Issues in vaccine development have been the complexity of multiple dengue serotypes in nature, the need to elicit good cross-dengue serotype responses, and incomplete understanding of protective parameters and their relation to disease severity. Specific issues with the Sanofi vaccine have been serotype-dependent efficacy of recent clinical trials, with higher DENV3 and DENV4 efficacy and lower DENV1 and DENV2 efficacy, when DENV1 and DENV2 were the more prevalent serotypes during an outbreak (Fig. 3). Whether the differential vaccine efficacy by serotype is due to prevalence of each serotype during an outbreak or due to strain differences remains to be explored. Original concerns over the potential for immune enhancement [17] (and thus a requirement for simultaneous efficacy against all four serotypes) did not materialize in the advanced dengue vaccine trials.

Ultimately, control of dengue will depend on a combined approach: vaccination, environmental management emphasizing vector study and control, and new antivirals as they become available.

Conclusion

Dengue is an important public health problem worldwide and recent studies have increased awareness and understanding of neurologic complications of infection. Given its epidemiology and the global factors that are supporting the alarming increase in numbers of dengue infections, total eradication of dengue is not likely, and neurologists will continue to have a role in recognition and care of patients. Because dengue affects more than one third of the world's population and treatment remains supportive at this time, efforts in pathogenesis, vaccines, antivirals, environmental risk reduction, and vector control are all critical for disease control.

Acknowledgments This work was, in part, supported by the Ministry of Education, Taiwan, R.O.C., The Aim for the Top University Project to the National Cheng Kung University (NCKU), and Ministry of Science and Technology Grant (MOST 102-2320-B-006–049) and (MOST 103-2320-B-006-030-MY3).

Compliance With Ethics Guidelines

Conflict of Interest Marylou V. Solbrig and Guey-Chuen Perng declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent Human study was approved by the University Committee of Institutional Revue Board of National Cheng Kung University and performed under protocol KMUH-IRB-960195.

References

Papers of particular interest, published recently, have been highlighted as
- • Of importance
- •• Of major importance

1. Soares CN, Cabral-Castro MJ, Peralta JM, et al. Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. J Neurol Sci. 2011;303:75–9.
2.•• Araujo FM, Araujo MS, Nogueira RM, et al. Central nervous system involvement in dengue: a study in fatal cases from a dengue endemic area. Neurology. 2012;78(10):736–42. **Clinical and neuropathologic study of neuroinvasive dengue.**
3.•• Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12:906–19. **One of the most comprehensive, current reviews on nervous system aspects of dengue virus infection.**
4. le Tan V, le Thai H, Phu NH, et al. Viral aetiology of central nervous system infections in adults admitted to a tertiary referral hospital in

Southern Vietnam over 12 years. PLoS Negl Trop Dis. 2014;8(8), e3127. doi:10.1371/journal.pntd.0003127. eCollection 2014.
5. Tarantola A, Goutard F, Newton P, et al. Estimating the burden of Japanese encephalitis virus and other encephalitides in countries of the Mekong delta. PLoS Negl Trop Dis. 2014;8(1), e2533. doi:10.1371/journal.pntd.0002533. eCollection 2014.
6. Solomon T, Dung NM, Vaughn DW, et al. Neurological manifestations of dengue infection. Lancet. 2000;355(9209):1053–9.
7. World Health Organization (WHO). Technical guide for diagnosis, treatment, surveillance, prevention, and control of dengue hemorrhagic fever. Geneva: WHO; 1982.
8. World Health Organization (WHO). Dengue haemorrhagic fever: diagnosis, treatment, prevention, and control. Geneva: WHO; 1997.
9. World Health Organization (WHO). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. WHO; 2009.
10.• Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7. **One of the most current data sets on dengue worldwide.**
11. Rodriguez-Roche R, Gould EA. Understanding the dengue viruses and progress towards their control. Biomed Res Int. 2013;2013: 690835. doi:10.1155/2013/690835.
12.• Graham AS, Pruszynski CA, Hribar LJ, et al. Mosquito-associated dengue virus, Key West, Florida, USA, 2010. Emerg Infect Dis. 2011;17(11):2074–5. **The report that raises the possibility of the return of epidemic dengue to the continental USA.**
13. Adalja AA, Sell TK, Bouri N, Franco C. Lessons learned during dengue outbreaks in the United States, 2001–2011. Emerg Infect Dis. 2012;18(4):608–14.
14. Radke EG, Gregory CJ, Kintziger KW, et al. Dengue outbreak in Key West, Florida, USA, 2009. Emerg Infect Dis. 2012;18(1):135–7.
15. Murray KO, Rodriguez LF, Herrington E, et al. Identification of dengue fever cases in Houston, Texas with evidence of autochthonous transmission between 2003 and 2005. Vector Borne Zoonotic Dis. 2013;13(12):835–45.
16. Waterman SH, Margolis H, Sejvar JJ. Surveillance for dengue and dengue-associated neurologic syndromes in the United States. Am J Trop Med Hyg 2014;14–0016.
17. Halstead SB. Dengue. Lancet. 2007;370(9599):1644–52.
18. Guzman MG, Kouri G. Dengue haemorrhagic fever integral hypothesis: confirming observations, 1987–2007. Trans R Soc Trop Med Hyg. 2008;102(6):522–3.
19. Meltzer E, Schwartz E. A travel medicine view of dengue and dengue hemorrhagic fever. Travel Med Infect Dis. 2009;7:278–83.
20. Chao DY, Lin TH, Hwang KP, et al. 1998 dengue hemorrhagic fever epidemic in Taiwan. Emerg Infect Dis. 2004;10:552–4.
21. Huy NT, Van Giang T, Thuy DH, et al. Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2013;7(9):e2414. doi:10.1371/journal.pntd.ooo2412.eCollection2013.
22. Matlani M, Chakravarti A, Rawal A, Kashyap B, Gurtoo A. Dengue encephalitis: an entity now common in dengue-prone regions. Trop Dr. 2009;39(2):115–6.
23. Rittmannsberger H, Foff C, Doppler S, Pichler R. Psychiatric manifestation of a dengue-encephalopathy [German]. Wien Klin Wochenschr. 2010;122(3):87–90.
24. Baldaçara L, Ferreira JR, Seixas Filho LCP, et al. Behavior disorder after encephalitis caused by dengue. J Neuropsychiatry Clin Neurosci. 2013;25(1):E44.
25. Srivastava S, Bhatia MS, Jhanjee A. Organic mania in dengue. J Clin Diagn Res. 2013;7:566–7.
26. Kalita J, Misra UK. EEG in dengue virus infection with neurological manifestations: a clinical and CT/MRI correlation. Clin Neurophysiol. 2006;117(10):2252–6.
27. Misra UK, Kalita J, Syam UK, Dhole TN. Neurological manifestations of dengue virus infection. J Neurol Sci. 2006;244:117–22.
28. Liou LM, Lan SH, Lai CL. Dengue fever with ischemic stroke: a case report. Neurologist. 2008;14(1):40–2.
29. Liou LM, Lan SH, Lai CL. Electroencephalography burst suppression in a patient with dengue encephalopathy: a case report. Clin Neurophysiol. 2008;119(10):2205–8.
30. Jha S, Ansari MK. Dengue infection causing acute hypokalemic quadriparesis. Neurol India. 2010;58(4):592–4.
31. Sharma CM, Kumawat BL, Ralot T, Tripathi G, Dixit S. Guillain-Barre syndrome occurring during dengue fever. J Indian Med Assoc. 2011;109(9):675–82.
32. Verma R, Sharma P, Khurana N, Sharma LN. Neuralgic amyotrophy associated with dengue fever: case series of three patients. J Postgrad Med. 2011;57(4):329–31.
33. Gutch M, Agarwal A, Amar A. Hypokalemic quadriparesis: an unusual manifestation of dengue fever. J Nat Sci Biol Med. 2012;3(1):81–3.
34. Ratnayake EC, Shivanthan C, Wijesiriwardena BC. Diaphragmatic paralysis: a rare consequence of dengue fever. BMC Infect Dis. 2012;12:46.
35. Jain RS, Handa R, Prakash S, Nagpal K, Gupta P. Acute hypokalemic quadriparesis: an atypical neurological manifestation of dengue virus. J Neurovirol. 2014;20(1):103–4.
36.•• Puccioni-Sohler M, Rosadas C, Cabral-Castro MJ. Neurological complications in dengue infection: a review for clinical practice. Arq Neuropsiquiatr. 2013;71(9B):667–71. **Key observations and review of laboratory diagnosis of dengue, including sensitivity and specificity of serum and CSF markers.**
37. Sahu R, Verma R, Jain A, et al. Neurologic complications in dengue virus infection: a prospective cohort study. Neurology. 2014;83(18):1601–9.
38. Hegde V, Aziz Z, Kumar S et al. Dengue encephalitis with predominant cerebellar involvement: report of eight cases with MR and CT imaging features. Eur Radiol 2014; PMID:25361825.
39. Mathew RP, Basti RS, Hegde P, et al. Rare case of acute dengue encephalitis with correlated MRI findings. J Med Imaging Radiat Oncol. 2014;58(6):679–82.
40. Bhoi SK, Naik S, Kumar S, et al. Cranial imaging findings in dengue virus infection. J Neurol Sci. 2014;342(1–2):36–41.
41. Yeo PSD, Pinheiro L, Tong P, et al. Hippocampal involvement in dengue fever. Singap Med J. 2005;46(11):647–50.
42. Wasay M, Channa R, Jumani M, et al. Encephalitis and myelitis associated with dengue viral infection clinical and neuroimaging features. Clin Neurol Neurosurg. 2008;110:635–40.
43. Malik R, Gogna A, Meher J, Singh KK, Sharma SK. Dengue encephalopathy—still an enigma? J Infect Dev Ctries. 2014;8(8): 1076–8.
44. Becerra A, Warke RV, Xhaja K, et al. Increased activity of indoleamine 2,3-dioxygenase in serum from acutely infected dengue patients linked to gamma interferon antiviral activity. J Gen Virol. 2009;90(Pt 4):810–7.
45. Wang Y, Liu H, McKenzie G, et al. Kynurenine is an endothelium-derived relaxing factor produced during inflammation. Nat Med. 2010;16(3):279–85.
46. Changsirivathanathamrong D, Wang Y, Rajbhandari D, et al. Tryptophan metabolism to kynurenine is a potential novel contributor to hypotension in human sepsis. Crit Care Med. 2011;39(12): 2678–83.
47. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest. 2007;117(5):1147–54.
48. Platten M, Wick W, van den Eynde BJ. Tryptophan catabolism in cancer: beyond IDO and tryptophan depletion. Cancer Res. 2012;72(21):5435–40.
49. Stone TW. Neuropharmacology of quinolinic and kynurenic acids. Pharmacol Rev. 1993;45:309–79.

50. Fukui S, Schwarcz R, Rapoport SI, et al. Blood–brain barrier transpost of kynurenines: implications for brain synthesis and metabolism. J Neurochem. 1991;56(6):2007–17.
51. Raison CL, Dantzer R, Kelley KW, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. Mol Psychiatry. 2010;15(4):393–403.
52. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry. 2007;12(11):988–1000.
53. Heyes MP, Saito K, Crowley JS, et al. Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. Brain. 1992;115:1249–73.
54. Baran H, Gramer M, Honack D, Loscher W. Systemic administration of kainate induces marked increases of endogenous kynurenic acid in various brain regions and plasma of rats. Eur J Pharmacol. 1995;286:167–75.
55. Baran H, Jellinger K, Deeck L. Kynurenine metabolism in Alzheimer's disease. J Neural Transm. 1999;106:165–81.
56. Scott RM, Nisalak A, Cheamudon U. Isolation of dengue viruses from peripheral blood leukocytes of patients with hemorrhagic fever. J Infect Dis. 1980;141(1):1–6.
57. Salazar MI, Perez-Garcia M, Terreros-Tinoco M et al. Dengue virus type 2: protein binding and active replication in human central nervous system cells. Sci World J 2013; 904067. doi:10.1155/2013/904067.eCollection2013
58. Puccioni-Sohler M, Soares CN, Papaiz-Alvarenga R, Castro MJ, Faria LC, Peralta JM. Neurologic dengue manifestations associated with intrathecal specific immune response. Neurology. 2009;73(17):1413–7.
59. Lin CF, Chiu SC, Hsiao YL, et al. Expression of cytokine, chemokine, and adhesion molecules during endothelial cell activation induced by antibodies against dengue virus nonstructural protein 1. J Immunol. 2005;174(1):395–403.
60. Alhoot MA, WSang SM, Sekaran SD. Inhibition of dengue virus entry ad multiplication into monocytes using RNA interference. PLoS Negl Trop Dis. 2011;5(11):e1410. doi:10.1371/journal.pntd.0001410.
61. Seet RCS, Quek AML, Lim ECH. Post-infectious fatigue syndrome in dengue infection. J Clin Virol. 2007;38(1):1–6.
62. Garcia G, Gonzalez N, Perez AB, et al. Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. Int J Infect Dis. 2011;15(1):e38–43.
63.•• Sinha G. Sanofi's dengue vaccine first to complete phase 3. Nat Biotechnol. 2014;32:605–6. **Excellent summary of vaccine progress, unmet needs, and future of dengue control.**
64.• Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomized, observer-masked, placebo-controlled trial. Lancet. 2014;384:1358–65. **Phase III human trial results of a candidate dengue vaccine.**
65.• Villar L, Dayan GH, Arredondo-Garcia J, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015;372(2):113–23. **Phase III human trial results of a candidate dengue vaccine.**
66. Leonard BE. The concept of depression as a dysfunction of the immune system. Curr Immunol Rev. 2010;6(3):205–12.