

Neurological Complications in a Polynesian Traveler with Dengue

Maegan L.M. Doi MD; Sydney Y. Tatsuno MD, FACP; Gurdev Singh MD, FRCS, FACP; Eric M. Tatsuno BS; and Marjorie M. Mau MD, MS, MACP

Abstract

In recent times, there has been an increased focus on mosquito-borne *Flaviviruses*, in particular dengue and Zika. With the reappearance of dengue in Hawai'i and the mainland United States (US), clinicians should be aware of both the common presentations of dengue, as well as other less common complications associated with the disease. Dengue can result in neurologic disorders such as encephalopathy, encephalitis, immune-mediated syndromes, neuromuscular dysfunction, and neuro-ophthalmologic disorders. We present an interesting case of dengue that initially presented with classic symptoms (arthropathy, biphasic fever, and rash) and subsequently developed into a neurologic movement disorder with muscle tightening and twitching of the face, chest, and extremities. We review and update the epidemiology, biology, the clinical presentations including the neurologic complications associated with dengue, as well as their management and areas of future study in this field.

Keywords

Dengue Virus, Dengue Fever, Flavivirus, Neuromuscular Complications of Dengue, Dengue in Hawai'i

Acronyms

Dengue Virus (DENV), Dengue Virus Serotypes (DENV -1, DENV -2, DENV -3, DENV -4), Non-Structural Protein 1 (NS1), Dengue - Reactive Immunoglobulin M (DENV - IgM) and Dengue - Reactive DENV Immunoglobulin G (DENV - IgG), World Health Organization (WHO), Medical Officer (MO), Status Post (S/P), White Blood Cell Count (WBC), Hemoglobin (Hgb), aspartate aminotransferase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), ribonucleic acid (RNA), Thyroid Stimulating Hormone (TSH), Complete Blood Count (CBC)

Introduction

Dengue is conservatively estimated to infect 50 million individuals throughout 100 countries on an annual basis, and appears to be increasing.¹ Some estimate 390 million new infections per year worldwide of which 96 million are symptomatic.² In 2015-2016, there was a dengue outbreak in Hawai'i with a reported 264 cases.

Dengue fever is caused by a *Flavivirus* and is transmitted to humans by mosquitoes. In Hawai'i, two species of mosquitoes, *Aedes aegypti* (*A. aegypti*) and *Aedes albopictus* (*A. albopictus*), are the known vectors responsible for transmission of the dengue virus.³ There are four dengue virus (DENV) serotypes (DENV - 1, DENV - 2, DENV - 3, DENV - 4), and infection from one serotype will provide lifelong immunity to that specific serotype; however, only partial and short-term immunity will be present to the other three serotypes.⁴ Laboratory testing is available through a rapid diagnostic test that identifies the non-structural protein 1 (NS1) viral antigen during the febrile phase, or DENV - reactive immunoglobulin M (IgM) and DENV - reactive immunoglobulin G (IgG) antibodies during the critical and recovery phases.^{1,4,5}

The febrile, critical, and recovery phases are three distinct phases associated with dengue fever infection. The symptoms present during the febrile phase are: high fever ($\geq 38.5^{\circ}\text{C}$), headache, vomiting, myalgia, joint pain, and in certain cases, macular rash. Additionally, mild hemorrhagic conditions such as petechiae and bruising, and a palpable liver are also present. During the critical phase, which can present between days four and seven following infection, a systemic vascular leak syndrome will present with the following symptoms: elevated hemoconcentration, hypoproteinemia, pleural effusions, ascites, persistent vomiting, severe abdominal pain, tender hepatomegaly, serosal effusions, mucosal bleeding, and lethargy or restlessness. The recovery phase is usually associated with rapid improvement in the patient's condition as the vascular permeability spontaneously improves to normal. Some patients may skip the critical phase and move from the febrile phase to the recovery phase. According to the World Health Organization (WHO), this is the classical form of dengue, also referred to as just dengue.¹ Severe dengue occurs when the patient experiences symptoms related to the critical phase. Most cases of dengue, however, are asymptomatic. It is believed that subsequent infections, either concurrent or divergent will increase the likelihood that the patient contracts severe dengue.⁴

Dengue and severe dengue have the potential to cause neurological complications, including dengue encephalopathy (caused by metabolic disorders or liver failure), encephalitis (caused by direct viral invasion), immune mediated syndromes, neuromuscular dysfunction (eg, Guillain-Barre) and neuro-ophthalmologic disorders with some overlap among the categories.⁶ We present a case of a 39-year-old Hawai'i resident who contracted dengue while on an ocean voyage in French Polynesia. She initially presented with the classical symptoms of dengue but subsequently developed neurological complications including twitching of her face, chest, and extremities and was diagnosed by her neurologist to have a neurological movement disorder. Considering the resurgence of dengue, clinicians in Hawai'i and the mainland US should be aware of the common classical presentations of dengue as well as the underreported neurological complications associated with this disease.

Case Presentation

A 39 year-old woman serving as a crew member on a traditional voyaging canoe presented to the on-board medical officer (MO) with a two-day history of nausea, diarrhea, and shaking chills. The previously healthy crew member came aboard the canoe in Pape'ete, Tahiti 14-days prior to her illness. The MO treated her empirically with ciprofloxacin for presumed traveler's diarrhea.

On Day Three she reported continued malaise and fatigue but declined any further medication. She was monitored frequently with temperature checks and on Day Four of her illness she was found to have a temperature of 99.8°F at 10 AM and re-checked at 1 PM with a temperature of 102.4°F and new symptoms of significant joint pain and muscle aches of both hands. She was treated with ibuprofen and her nausea and symptoms subsided to the point that she was feeling well enough to participate in voyaging land activities (celebrations, cultural protocols, etc). Day Five of the illness was notable for the voyaging canoe as it set sail for a 620 nautical mile open-ocean sail. After the canoe set sail, the crew member reported recurrence of her nausea, malaise, fatigue, and intermittent low grade fevers. On Days Five and Six of the patient's illness, she was unable to take oral hydration adequately with worsening malaise, weakness, and fatigue and was placed in "sick bay" to be monitored by the on-board MO. On Day Seven, the patient's status continued to decline, as her condition was marked by dehydration for two days while on open-ocean sailing, temperatures ranging from 99.4-100.0 °F with mild tachycardia (90s bpm), blood pressure 100/60 mmHg, and signs of dry mucus membranes and poor skin turgor. A presumptive diagnosis of acute dengue fever exacerbated by dehydration was made by the MO and supportive treatment including intravenous fluids were administered. As a result of the supportive treatment, the patient's vital signs responded well with a blood pressure of 120/82 mmHg and her low grade fever was responsive to acetaminophen. On Days Seven and Eight, the patient's clinical course improved and then relapsed throughout the 48 hour period despite supportive care on-board by the MO. At the end of Day Eight, the voyaging canoe captain in consultation with the MO decided to activate a medical evacuation plan for the patient to allow appropriate clinical management and stabilization. The patient, accompanied by the MO, was evacuated to Mitiaro Island then flown to Rarotonga Island, New Zealand and taken directly to an urgent care clinic. The Rarotonga physician agreed with the MO's presumptive diagnosis of acute dengue fever and laboratory tests were obtained. The patient was placed in home quarantine pending results, and on Day Nine the patient noticed a rash of diffuse erythematous macular lesions over her back, neck, abdomen, and palms.

The patient's past medical history was significant only for Grave's disease, status post (S/P) 131-I ablation more than 1 year ago and stable on replacement doses of levothyroxine. The rest of the patient's medical records as well as her social and family history were unremarkable.

Laboratory tests performed at the Rarotonga urgent care clinic facility revealed a low white blood cell count (WBC) 2.5×10^9 cells/liter (normal 4.0-14.5 $\times 10^9$ cells/liter), elevated hemoglobin (Hgb) 16.6 g/dL (normal 11.5-15.5 g/dL), low platelets 68×10^9 cells/liter (normal 150-400 $\times 10^9$ cells/liter) with a neutropenia of 0.6×10^9 on differential. Liver function tests were elevated 2-3X the upper limit of normal with aspartate aminotransferase (AST) 103 units per liter (U/L) (normal female <32 U/L), alanine transaminase (ALT) 63 U/L (normal

female <31 U/L); gamma glutamyl transferase (GGT) 82 U/L (normal female 7-32 U/L) and total bilirubin 20 micromol/L (normal <19 micromol/L). Blood samples were sent for a viral ribonucleic acid (RNA) antigen "quick test" for dengue antigen and IgM antibodies. Both tests were reported as "positive" within 24 hours and samples were sent to a reference laboratory for confirmation. The patient was placed on home restrictions while in Rarotonga and subsequently flown back to Hawai'i on Day Nine of the onset of her illness. A second blood test was obtained 11 days post-acute dengue fever illness by the patient's primary care provider in Hawai'i. The serology was sent to a certified reference laboratory (Focus Diagnostics) and revealed elevated titers of dengue IgM 9.77 (normal <0.90) and dengue IgG 2.3 (normal <0.90).

Approximately two weeks after the onset of her symptoms the patient reported the development of new involuntary "muscle tightening and twitching" of face, chest, and extremities. A laboratory work up was completed and the results were normal including a normal thyroid stimulating hormone (TSH) and the patient was referred to a neurologist for consultation. The patient was seen by the neurologist who made a presumptive diagnosis of mild neuromuscular complications of dengue disease. The neurologist did not recommend any specific treatment intervention but recommended continued observation instead. Additional laboratory tests including a complete blood count (CBC) with differential, sedimentation rate and creatine phosphokinase were ordered and were normal. The patient did not undergo any imaging tests, and her neurological symptoms eventually resolved without specific therapy over the next six months.

Discussion

We present a case of classic dengue, which presented initially with the common manifestations of dengue including arthropathy, biphasic fever, and rash. Serological testing for dengue was positive. However, 14 days after she presented with her initial symptoms she started to experience neurological complications including muscle tightening and twitching of her face, chest, and extremities. She was evaluated by a neurologist who confirmed a neurological movement disorder.

The exact extent of neurological complications associated with dengue are not known but are rarely reported,⁷ some estimating it at 1%.⁶ Many of the reports are in the international journals and some of the major textbooks and references do not even make mention of the neurological complications of dengue. Considering the recent outbreak of dengue fever in Hawai'i in 2015-2016 and the increase in global travel, clinicians need to be aware of not only the more classic presentation of dengue, including fever, retro orbital headache, and body aches, the so called "break bone fever," but also some of the neurological presentations.

Neurological complications of dengue disease can be categorized into dengue encephalopathy, encephalitis caused by direct viral invasion, immune mediated syndromes, neuromuscular dysfunction for example Guillain Barré and neuro-ophthalmo-

logical disorders. Furthermore, there may be some overlap, and some of the neurological manifestations may not fit neatly into any one particular category.⁶

Acute encephalopathy manifests itself with diminished level of consciousness and is the most common reported neurological disorder associated with dengue.⁸ It may be caused by hypotension, anoxia, metabolic disorders including hyponatremia, cerebral hemorrhage, edema and acute liver or renal failure, and the cerebrospinal fluid analysis is normal. Encephalitis is secondary to the direct central nervous system invasion of the virus and may present similar to encephalopathy including altered mental status and seizures, however, the cerebrospinal fluid analysis is abnormal. Immune mediated syndromes include post dengue acute transverse myelitis with urinary retention and lower extremity numbness, which can arise one to two weeks after the onset of symptoms. Neuro-ophthalmological complications usually involve the posterior segment and include visual disturbance secondary to retinal vasculopathy and optic neuropathy.⁶ A case of dengue with papilledema has been reported.⁹

Neuromuscular complications of dengue as reported in this case are relatively rare. They are only sporadic cases being reported worldwide. Cases of Guillain Barré¹⁰ including Miller-Fisher syndrome have been reported along with other forms of motor weakness¹¹ including rhabdomyolysis¹² and hypokalemic periodic paralysis.¹³ Abducens nerve palsy¹⁴ as well as opsoclonus myoclonus syndrome have been reported.¹⁵ Strokes, especially hemorrhagic stroke symptoms have been reported because of the coagulopathy associated with dengue fever.¹⁶ More recently in 2016 a case of a rhombencephalitis associated with dengue fever was reported,¹⁷ two cases of thalamic and basal ganglia involvement associated with dengue were also reported.⁷

Clinicians confronted with patients that have had febrile episodes with neurological complications, especially if they have traveled to an endemic area should have dengue in the differential diagnosis. Also included in the differential diagnosis should be malaria, measles, meningococemia, typhoid and paratyphoid fever, leptospirosis, the viral hemorrhagic fevers, and Chikungunya.⁴ The Zika virus which is in the same genus as the dengue virus, the Flaviviruses, has been reported to cause similar neurological complications including an outbreak of Guillain – Barré in French Polynesia.¹⁸ More alarmingly for Hawai'i, the same mosquitoes species that spread dengue are also responsible for the spread of Zika.

Given the rapid spread of these arthropod borne illnesses including dengue, Zika, and Chikungunya worldwide, novel public health approaches outside of the traditional vector control is needed. A dengue vaccine produced by Sanofi-Pasteur labeled CYD-TDV is the most promising but does have some potential concerns.^{19,20} Research involving bacteria called *Wolbachia* has found that the dengue virus cannot replicate in mosquitoes infected with this bacteria and infected mosquitoes produce offspring that do not transmit the dengue virus to humans.²¹ Currently, there are no effective antivirals. Considering the looming arbovirus pandemics, including dengue and Zika, a one-bug-one-drug approach appears inadequate and research should be geared to broad-spectrum antiviral drugs instead.²² A recent report summarizes the need for an integrated multi-pronged approach.²³

Conclusion

There has recently been a significant worldwide spread of diseases due to the mosquito-borne Flaviviruses, in particular Dengue and Zika. Patients may present with important, and less commonly reported, complications of these diseases. The neurological complications associated with dengue are rare and many of the case reports on the neurological complications associated with dengue are published in international journals. Due to the recent resurgence of dengue in Hawai'i and the increase in international travel, it is pertinent for all health care providers in the State to be familiar with both the common presentations of dengue and the unique manifestations, such as the neurological complications. For this reason we described a case of dengue virus infection with neurological complications, reviewed the clinical presentations, epidemiology, biology, management, and recommended areas for future investigation.

Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgement

Dr. Mau was supported under NIH grant: NIMHD, P20 MD 000173.

Authors' Affiliation:

- University of Hawai'i, John A. Burns School of Medicine, Honolulu, HI

Correspondence to:

Sydney Y. Tatsuno MD; Email: sydtatsuno@gmail.com

References

1. Simmons CP, Farrar JJ, Nguyen VV, Wills B. Dengue. *N Eng J Med*. 2012; 366:1423-1432.
2. Bhatt S, Gething P, et al. The global distribution and burden of dengue. *Nature*. 2013;496:504-507.
3. Winchester J, Kapan D. History of Aedes Mosquitoes in Hawaii. *Journal of the American Mosquito Control Association*. 2013;29:154-163.
4. Medecins Sans Frontieres. *Clinical guidelines diagnosis and treatment manual*. 2016; 213-219. Retrieved from: http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf.
5. Centers for Disease Control. Laboratory guidelines and diagnostic testing for dengue fever. Retrieved from: <https://www.cdc.gov/dengue/clinlab/lab/laboratory.html>.
6. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complication of dengue virus infection. *Lancet Neuro*. 2013;12:906-919.
7. Liyanage, G, Adhikari L, et al. Two case reports on thalamic and basal ganglia involvement in children with dengue fever. *Case Reports in Infectious Disease*. 2016;1368:1-3.
8. Verma R, Sahu R, Holla V. Neurological manifestations of dengue infection: A review. *J Neurol Sci*. 2014;346:26-34.
9. Tahir M, Gupta E, et al. Dengue fever with papilledema: a case of dengue-3 virus in central nervous system. *Journal of Clinical Virology*. 2006;37:65-67.
10. Gupta P, Jain V, Chatterjee S, Agarwal AK. Acute inflammatory motor axonopathy associated with dengue fever. *JACM*. 2009;10:58-59.
11. Misra UK, Kalita, J. Spectrum of neurological manifestations of dengue in India. *Dengue Bulletin*. 2006;30:107-113.
12. Lim M, Goh HK. Rhabdomyolysis following dengue virus infection. *Singapore Med J*. 2005;46:645-646.
13. Gutch M, Agarwal A, Amar A. Hypokalemic quadriplegia: An unusual manifestation of dengue fever. *J Nat Sci Biol Med*. 2012;3:81-83.
14. Shivanthan MC, Ratnayake EC, Wijesiriwardena BC, Somaratna KC, Gamagedara LK. Paralytic squint due to abducens nerve palsy: A rare consequence of dengue fever. *BMC Infect Dis*. 2012;12:156.
15. Verma R, Sharma P, Garg RK, Atam V, Singh MK, Mehrotra HS. Neurological complications of dengue fever: Experience from a tertiary center of north India. *Ann Indian Acad Neurol*. 2011;14:272-278.
16. Kumar J, Kumar A, Gupta S, Jain D. Dengue haemorrhagic fever: an unusual cause of intracranial haemorrhage. *J Neurol/Neurosurg Psychiatry*. 2007;78:253.
17. Verma R, Bharti K, Mehta, M, Bansod A. Rhombencephalitis associated with dengue fever. *Journal of Clinical Virology*. 2016;78:99-101.
18. Cao-Lormeau VM, Blake A, et al. Guillain-Barre syndrome outbreak associated with Zika virus infection in French Polynesia: a case control study. *Lancet*. 2016;387:1531-1539.
19. Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, Muhammad Ismail HI, Reynales H, Limkittikul K, Rivera-Medina DM, et al. Efficacy and long-term safety of dengue virus vaccine in the regions of endemic disease. *N Eng J Med*. 2015;373:1195-1206.
20. Simmons CP. A candidate dengue vaccine walks a tightrope. *N Eng J Med*. 2015;373:1263-1264.
21. O'Neill S. How a tiny bacterium called Wolbachia could defeat dengue. *Scientific American*. 2015.
22. Fauci AS, Morens DM. Zika virus in the Americas-Yet another arbovirus threat. *N Eng J Med*. 2016;374:601-604.
23. Pang T, Mak T, Gubler D. Prevention and control of dengue-the light at the end of the tunnel. *Lancet*. Retrieved from: [http://dx.doi.org/10.1016/S1473-3099\(16\)30471-6](http://dx.doi.org/10.1016/S1473-3099(16)30471-6).