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A Case Series of Three US Adults with Japanese Encephalitis, 2010-2012

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Abstract

Background—Japanese encephalitis (JE) virus is the leading vaccine-preventable cause of encephalitis in Asia. Although the risk for JE for most travelers to Asia is low, it varies based on the destination, season, trip duration, and activities.

Methods—We present case reports for three US adults who were infected with JE virus while traveling or residing in Asia.

Results—Among the three JE cases, one case had a 10-day trip to mainland China and participated in outdoor activities in a rural area, a second case had been resident in Taiwan for 4 months, and a third, fatal case was an expatriate living in South Korea.

Conclusions—JE should be considered in the differential diagnosis for any patient with an acute neurologic infection who recently has been in a JE-endemic country. Health-care providers should assess the itineraries of travelers to JE-endemic countries, provide guidance on personal protective measures to prevent vector-borne diseases, and consider recommending JE vaccine for travelers at increased risk for JE virus infection.

Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is the leading vaccine-preventable cause of encephalitis in Asia. There are an estimated 67,900 JE cases each year in endemic areas.[1] Although encephalitis develops in <1% of people infected with JE virus, among those who develop disease the first symptoms appear 5 to 15 days after the bite of an

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Declaration of Interests

The authors state they have no conflicts of interest to declare.

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infected mosquito. Outcome is often severe with a case-fatality rate of 20%-30% and sequelae among 30-50% of survivors.[2]

JE virus is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds. The main mosquito vector, *Culex tritaeniorhynchus*, commonly breeds in rice fields and pools of stagnant water and most often feeds outdoors during the evening and night.[3] The incidence of JE is highest in rural, agricultural areas.

The risk for JE for most travelers to Asia is low, but varies based on the destination, season, trip duration, and activities.[2,4] JE cases in travelers are rare, but case information can improve understanding of JE epidemiology and risks, and assist with development or refining of recommendations for preventive measures for travelers. We report three JE cases that occurred in 2010-2012 among US adults who traveled to or lived in Asia.

Case Reports

Case 1

In August 2010, a previously healthy man aged 33 years returned to the United States following a 10-day vacation to China. He was based in Shanghai, but had three trips, each of about 2 days duration, to three outlying areas: Zhejiang Province, Anhui Province, and a third unspecified destination. During at least one of his side trips he participated in outdoor activities, including swimming and hiking. He stayed in air-conditioned, screened accommodations for the duration of his trip. He had not received JE vaccine or any other vaccines prior to travel.

The patient first noted a headache during his last week in China. Three days after his return to the United States, his roommate found him confused, with slurred speech and difficulty walking. In the emergency room, he complained of headache, and was disoriented, unable to follow commands, and having hallucinations. His examination was notable for fever (101.3°F [38.5°C]), neck stiffness, ataxia, and increased muscle tone. Lumbar puncture revealed an opening pressure of 30 cmH_20 (normal: 7 –18cmH_20). Cerebrospinal fluid (CSF) showed pleocytosis (98 white blood cells [WBC]/mm^3 [normal: 0–5/mm^3] with 65% lymphocytes and 30% monocytes), 4 red blood cells (RBC)/mm^3 (normal: 0 RBC/mm^3), elevated protein (63 mg/dL [normal: 15-45 mg/dL]), and normal glucose concentrations. His peripheral WBC count was 19,700/mm^3 (normal: 3,900—11,700/mm^3). Urine toxicology screening was negative. Brain magnetic resonance imaging (MRI) performed 2 days after admission showed T2 hyperintensities in the deep gray nuclei as well as possible subacute infarcts in the right thalamus and midbrain.

The patient was treated empirically with broad-spectrum antibacterial agents and acyclovir. He gradually improved and was discharged on hospital day 14. At 8 months after discharge, he was reported to be fully recovered with no sequelae.

CSF collected on admission and serum collected 4 days after admission tested positive for JE virus-specific immunoglobulin (Ig) M antibodies by Centers for Disease Control and Prevention (CDC) enzyme-linked immunosorbent assay (ELISA); results were confirmed by plaque reduction neutralization testing (PRNT). Testing for other etiologies was negative,

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including CSF IgM antibodies to other arboviruses endemic to Asia, CSF bacterial cultures, and polymerase chain reactions (PCR) for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, enterovirus, and human herpesvirus 6.

Case 2

During June 2011, a previously healthy 61 year old US citizen was hospitalized with fever, confusion, and mental status changes. His illness commenced 1 day after arriving back in the United States from 4 months teaching in western Taiwan. He lived in a screened, air-conditioned house in Taiwan and had not traveled in the 2 weeks prior to his illness. He reportedly had not participated in activities such as camping or hiking that could have increased his risk of mosquito bites. He had not received JE vaccine prior to his travel.

The patient presented to hospital with fever (101°F [38.3°C]) and confusion. His peripheral WBC count was normal (10,300/mm^3) but CSF showed a pleocytosis (147 WBC/mm^3 with 50% lymphocytes and 26% polymorphonuclear leukocytes), elevated protein (127 mg/dL), and normal glucose concentrations. The patient was treated empirically with antibacterial agents, acyclovir, and intravenous immunoglobulin, and admitted to the intensive care unit. A brain computed tomography (CT) scan showed no acute intracranial findings. The patient's mental status slowly improved and he was discharged on hospital day 8 with no sequelae.

CSF collected on day 2 and serum collected on day 3 of illness showed JE virus-specific IgM and neutralizing antibodies in testing by CDC ELISA and PRNT. Other tests were negative, including bacterial culture, herpes simplex virus PCR, leptospirosis serology, and testing by IgM ELISA and PRNT for other arboviruses found in Asia, including dengue and chikungunya viruses.

Case 3

In August 2012, a 42 year old US citizen presented to a hospital in South Korea with respiratory distress and altered mental status. The patient lived approximately 65 km south of Seoul; he had resided in South Korea since 2009 and had not traveled out of the country since then. He had not received JE vaccine but had received yellow fever vaccine in the past.

The patient had onset of a febrile illness several days prior to hospitalization which progressed to include altered behavior and difficulty breathing. At presentation, key findings included tachycardia, respiratory distress, diffuse rhonchi on pulmonary auscultation, and an inability to verbalize, squeeze with the left hand, or move the left leg. CSF showed pleocytosis (16 WBC/mm^3 with 74% lymphocytes), 7 RBC/mm^3, elevated protein (62mg/dL), and normal glucose. CT scan showed a hypodensity in the right temporal lobe and possible involvement of the right inferior thalamic region. The patient was initially treated with antibacterial agents and corticosteroids. However, his mental status deteriorated requiring mechanical ventilation and transfer to another facility. There his treatment included antibacterial agents, immunoglobulin, and plasmapheresis. A brain MRI on hospital day 22 showed multifocal and diffuse increased signal intensity with partial enhancement including in the bilateral basal ganglia, thalamus, and cerebral cortex,

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consistent with meningoencephalitis. His condition did not improve and he died 58 days after admission.

A serum sample collected the day after hospitalization had JE virus-specific IgM antibodies detected by ELISA. Acute and convalescent serum samples collected the day after admission and 29 days later showed a >4-fold rise in JE virus antibody titers by indirect immunofluorescence assay (IFA) performed at the South Korea National Institute of Health.

Discussion

JE is a serious but rare disease among travelers. The three cases described here represent the 6th, 7th, and 8th cases of JE reported in US citizens since JE vaccine became available in the United States in 1993.[5] These cases represent all cases reported to CDC since August 2010; however, cases may have been missed due to under-diagnosis, under-reporting, or if case diagnosis occurred overseas. Overall, 19 JE cases in US citizens have been reported in the literature since 1973 among a global total of 68 JE cases in travelers or expatriates from non-endemic countries published or reported to CDC.[4,6-14]

For two of the cases reported here, JE virus infection was confirmed by detection of JE virus-specific IgM and neutralizing antibodies in CSF. For the third case, JE virus-specific IgM antibodies were detected by ELISA in serum, but no JE testing was conducted on CSF. A fourfold rise in JE virus antibodies was detected by IFA; however, the patient had received plasma and immunoglobulin and a treatment-related increase in antibody titer cannot be excluded. Diagnosis of JE virus infections can be difficult. Serologic assays can provide false-positive results due to cross-reactive antibodies from other flavivirus infections or vaccines (e.g., dengue, tick-borne encephalitis, West Nile, or yellow fever viruses).[15] Receipt of immune globulin or other blood products can also complicate interpretation of laboratory results. Detection of JE virus-specific IgM antibodies in CSF suggests recent central nervous system infection, and cross-neutralization testing provides the best evidence of virus-specific antibodies; however, to interpret JE laboratory results in travelers, information regarding other circulating flaviviruses at the destination, previous flavivirus infections, immunization history, and any treatments with blood or blood products should be considered.

The overall incidence of JE among persons from non-endemic countries traveling to Asia is estimated to be less than one case per 1 million travelers.[2,4] However, the risk for JE among expatriates and travelers who stay for prolonged periods in endemic areas is likely higher. Among 37 travel-associated JE cases included in a recent review, 24 (65%) spent ≥1 month in JE risk areas.[4] Travelers on brief trips might be at increased risk of infection if they have extensive outdoor or nighttime exposure in rural areas. Among the 13 (35%) travelers in the series who stayed <1 month, three (23%) spent the majority of their time in rural areas, six (46%) stayed in coastal or non-rural areas but took day trips to rural areas or national parks, and one (8%) stayed in a coastal area and took day trips to unspecified destinations; no exposure-related information was available for three (23%) travelers. No cases were reported among short-term travelers who visited only urban areas.

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The short-term traveler described in this report was based in an urban area, but took at least one overnight trip to a rural area where he was involved in outdoor activities including hiking and swimming, thereby increasing his risk of exposure to mosquito bites. His travel was during China's peak JE virus transmission season.[16] The other two patients were residing in countries (Taiwan and South Korea) with comprehensive national JE immunization programs.[1,17] As a result, few cases occur among the local population and disease risk may be less apparent than in some other JE-endemic countries. However, because JE virus is maintained in nature in an animal-mosquito cycle, non-immune travelers or expatriates remain at risk for infection.

When providing advice to travelers on JE preventive measures, each person's specific itinerary, activities, duration, and season of travel must be considered. Risk assessments can be difficult, and factors such as tolerance for risk and willingness to adhere to mosquito precautions might be relevant. Recommendations for JE vaccine weigh the overall low risk for travel-associated JE disease, the lack of treatment, high mortality and morbidity when JE does occur, the risk (albeit low) for serious adverse events following vaccination, and the high cost of the vaccine. The U.S. Advisory Committee on Immunization Practices recommends JE vaccine for travelers who plan to spend ≥1 month in endemic areas during the JE virus transmission season. JE vaccine also should be considered for short-term travelers (<1 month) if they plan to travel outside of an urban area and will participate in activities that will increase their risk of JE virus exposure (e.g., camping, hiking, fishing), travelers to an area with a JE outbreak, and travelers uncertain of their itinerary or activities.[2] All travelers, regardless of duration of travel or vaccination status, should be advised of the importance of personal protective measures to reduce the risk for mosquito bites, including use of insect repellent, permethrin-impregnated clothing, and staying in accommodations with air-conditioning or screens.

None of the three JE cases described here, nor any JE cases in previously-published reports, were known to have received JE vaccine. Obstacles to use of JE vaccine in US travelers include its high cost and need for two doses prior to departure. A recent survey among US travelers to Asia assessed compliance with JE vaccine recommendations. Among 1,691 participants, 415 (25%) described itineraries for which JE vaccination should have been considered, but only 47 (11%) of these 415 higher JE risk travelers reported receiving ≥1 dose of JE vaccine.[18] Of the 164 unvaccinated higher JE risk travelers who visited a health-care provider before their trip, 113 (69%) indicated that they had never heard of JE vaccine or their health care provider had not offered or recommended JE vaccine. Those findings and these case reports underscore the need for health-care providers to understand the risks for JE disease among travelers and the measures available to prevent it, including use of JE vaccine according to recommendations.

JE should be considered in the differential diagnosis for any patient with an acute neurologic infection who recently has been in a JE-endemic country. Travelers and expatriates should ensure they are familiar with disease risks at their destination and preventive measures to reduce the risks. Health-care providers should assess the itineraries of travelers visiting JE-endemic countries, advise of the risk for JE virus infection, provide guidance on personal

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protective measures to prevent vector-borne diseases, and consider recommending JE vaccine for travelers at increased risk for JE virus infection.

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References

1. Campbell GL, Hills SL, Fischer M, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ. 2011; 89:766–74E. [PubMed: 22084515]
2. Centers for Disease Control and Prevention. Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010; 59:RR-1, 1–27.
3. Buescher EL, Scherer WF, Rosenberg MZ, et al. Ecological studies of Japanese encephalitis virus in Japan. II. Mosquito infection. Am J Trop Med Hyg. 1959; 8:651–64. [PubMed: 13805722]
4. Hills SL, Griggs AC, Fischer M. Japanese encephalitis in travelers from non-endemic countries, 1973–2008. Am J Trop Med Hyg. 2010; 82:930–936. [PubMed: 20439978]
5. Centers for Disease Control and Prevention. Inactivated Japanese encephalitis virus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1993; 42(RR-1)
6. Centers for Disease Control and Prevention. Japanese encephalitis in two children--United States, 2010. MMWR Morb Mortal Wkly Rep. 2011; 60:276–8. [PubMed: 21389931]
7. Jeurissen A, Strauven T. A case of aseptic meningitis due to Japanese encephalitis virus in a traveller returning from the Philippines. Acta Neurol Belg. 2011; 111:143–5. [PubMed: 21748935]
8. Tappe D, Nemecek A, Zipp F, et al. Two laboratory-confirmed cases of Japanese encephalitis imported to Germany by travelers returning from Southeast Asia. J Clin Virol. 2012; 54:282–5. [PubMed: 22465340]
9. Werlinrud AM, Christiansen CB, Koch A. Japanese encephalitis in a Danish short-term traveler to Cambodia. J Travel Med. 2011; 18:411–3. [PubMed: 22017718]
10. Langevin S, Libman M, Drebot MA, Laverdière M. A case of Japanese encephalitis virus infection acquired during a trip in Thailand. J Travel Med. 2012; 19:127–9. [PubMed: 22414040]
11. Lee DW, Choe YJ, Kim JH, et al. Epidemiology of Japanese encephalitis in South Korea, 2007-2010. Int J Infect Dis. 2012; 16:e448–52. [PubMed: 22497964]
12. National Notifiable Diseases Surveillance System, Australia. Notification rates of diseases, 1 January to 31 March 2012, by state or territory. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3602-pdf-cnt.htm/$FILE/cdi3602g.pdf. Accessed September 12, 2013
13. Doti P, Castro P, Martinez MJ, et al. A case of Japanese encephalitis in a 20 year-old Spanish sportsman, February 2013. Euro Surveill. 2013; 18(35)
14. Lagarde S, Lagier JC, Charrel R, et al. Japanese encephalitis in a French traveler to Nepal. J Neurovirol. Jan 10.2014 [Epub ahead of print].
15. Martin DA, Muth DA, Brown T, et al. Standardization of immunoglobulin M capture enzyme-linked immunosorbent assays for routine diagnosis of arboviral infections. J Clin Microbiol. 2000; 38:1823–6. [PubMed: 10790107]
16. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2014. Oxford University Press; New York: 2014.
17. Centers for Disease Control and Prevention. Japanese encephalitis surveillance and immunization — Asia and the Western Pacific, 2012. MMWR. 2013; 62(33):658–62. [PubMed: 23965828]

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18. Duffy MR, Reed C, Edelson PJ, et al. A survey of US travelers to Asia to assess compliance with recommendations for the use of Japanese encephalitis vaccine. J Travel Med. 2013; 20:165–70. [PubMed: 23577862]