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Case report

Two laboratory-confirmed cases of Japanese encephalitis imported to Germany by travelers returning from Southeast Asia

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ABSTRACT

Japanese encephalitis virus is the leading cause of encephalitis in Asia and parts of the Pacific. Despite the high number of symptomatic infections in endemic countries, clinical disease in travelers is rare. However, an increasing number of imported infections from popular holiday destinations in Southeast Asia have been recorded in the past few years, including serious disease courses in short-term travelers. Here we report two severe, non-fatal cases in tourists, who returned from a long-time stay in Thailand and a short-term trip to Bali, Indonesia, respectively. Recommendations for vaccination and pre-travel advice are discussed.

1. Why these cases are important

Japanese encephalitis (JE) is a severe and debilitating flavivirus infection occurring in large parts of Asia. The causative agent of JE, Japanese encephalitis virus (JEV), is a member of the family Flaviviridae and is transmitted by *Culex* mosquitoes. It is considered to be one of the most frequent causes of encephalitis in the world, reflecting the large number of people being exposed in highly populated areas, and is certainly the leading cause of vaccine-preventable encephalitis in Asia and regions of the Pacific.[1] The virus is maintained in a natural enzootic cycle by infected mosquitoes and waterbirds forming the natural animal reservoirs and an additional epizootic/epidemic transmission cycle involving pigs as amplifying vertebrate hosts. Transmission of JEV follows a seasonal pattern in temperate regions, leading to large outbreaks. In tropical areas, transmission is year-round, peaking during the rainy season.[2] The principal vector, *Culex tritaeniorhynchus*, a night active out-door biting mosquito, breeds in rice fields, and the risk of human infections is greatest in rural regions. Occasional infections are also reported from urban areas.[1] An estimated 3 billion people are at risk for JEV infection,[3] and JE has extended its geographical range from Asia to the South Pacific and Northern Australia.[4,5] Based on the viral envelope (E) gene, JEV is divided into 5 genotypes which have a different geographical distribution.[6] It has been suggested, however, that all known genotypes originated in the Indonesia–Malaysia region.[7]

Depending on age, less than 1% of human JEV infections develop clinical symptoms,[8] but in those cases mortality reaches 15–40%.[3] The incubation period is about 2 weeks after which most patients show sudden onset of fever and headache. Signs of meningeal irritations develop from the second day of illness, rapidly followed by cerebral symptoms.[3] In those who recover, a high rate of sequelae is recorded, and *restitutio ad integrum* is seen in only one third of patients with overt disease.[3] Despite the high number of clinical infections in endemic countries, reports on JE in travelers are rare.

We here report on two recent cases of severe, non-fatal JE acquired by German tourists during a long-term stay in Thailand, and a short-term holiday on the island of Bali, Indonesia, respectively. In the patients, acute concomitant urological and abdominal conditions were present.

2. Case descriptions

2.1. Case 1

On March 24, 2010, a 76-year-old male traveler was admitted to the neurological department of the University Medical Center of

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Table 1
Flavivirus serology results (indirect immunofluorescence assays) from patient 1 after long-term stay in Thailand.

Samples taken after disease onset	Case 1					
(days)	Serum			CSF		
	4	24	28	4	24	28
Anti-JEV-IgG	1:320	1:10,240	1:40,960	1:10	1:40	1:40
Anti-JEV-IgM	1:320	1:5120	1:1280	1:20	1:10	1:10
Anti-WNV-IgG	1:320	1:320	1:320	1:20	<1:10	<1:10
Anti-WNV-IgM	1:80	<1:20	<1:20	<1:10	<1:10	<1:10
Anti-TBEV-IgG	1:80	1:80	1:160	n.d.	<1:10	n.d.
Anti-TBEV-IgM	<1:20	<1:20	<1:20	n.d.	<1:10	n.d.
Anti-DENV-IgG	1:80	1:80	1:80	<1:10	<1:10	<1:10
Anti-DENV-IgM	<1:20	<1:20	<1:20	<1:10	<1:10	<1:10

CSF, cerebrospinal fluid; DENV, dengue virus; JEV, Japanese encephalitis virus; WNV West Nile virus; TBEV, tick-borne encephalitis virus. n.d., not done. Titers <1:20 for serum and <1:10 for CSF are considered negative.[20]

Mainz, Germany, after the return from a long-term stay in Thailand 2 days before. He had stayed for three months in the villages of Tak and Messot 50 km north of Bangkok, and had visited the surrounding area frequently. On admission, the patient reported that he had experienced several episodes of lower limb weakness and consecutive falls without losing consciousness at home. The past medical history was, apart from a history of infection with hepatitis B virus, unremarkable. The physical examination revealed a body temperature of 41 °C, psychomotor retardation and disorientation to time and place. There were no focal neurological deficits. Laboratory investigations showed elevated CK values (6015 U/l, normal <200 U/l) which were attributed to the multiple falls, and initially a slightly raised C-reactive protein level (0.67 mg/dl, normal <0.5 mg/dl) with an increase to 4.9 mg/dl in the next two days. Liver enzymes were elevated with an AST of 131 U/l (normal <35 U/l). White blood count revealed a leukocytosis of 18,200/μl. Red blood count showed low erythrocyte numbers of 4.13/pl (normal 4.2–5.6/pl), a decreased hemoglobin concentration of 11.9 g/dl (normal 13.5–17.5 g/dl) and a hematocrit of 33.4% (normal 39–49%), due to fluid resuscitation. Platelet count was normal. In addition, the patient complained of intense left-sided abdominal pain. An abdominal computed tomography (CT) revealed a dilated ureter, and a pigtail catheter was inserted. Antibiotic therapy was started with ceftriaxone and amoxicillin, combined with acyclovir. Two days after admission, the patient was still disorientated to the situation and showed word finding difficulties. He developed meningism on the following day and a cranial CT was performed, which showed no signs of ischemia or bleeding. The EEG revealed generalized slowing with accentuation on the right hemisphere three days later. Cerebrospinal fluid (CSF) analysis showed pleocytosis (137 leukocytes/μl, mainly activated lymphocytes and monocytes) one day after admission with an elevated CSF/serum albumin ratio of 11.27 (normal <9), a CSF/serum IgM ratio of 4.9, and a CSF/serum IgG ratio of 5.9 (normal <4.5), diagnostic for an increased blood-brain barrier permeability and intrathecal antibody production.

Based on the clinical presentation and the laboratory findings, a viral meningo-encephalitis was assumed. Serum antibody testing for acute infection with CMV, EBV, HSV, VZV, adenovirus, enterovirus, chikungunya virus, and *Mycoplasma pneumoniae* was negative. Serological results for a flavivirus infection were positive (Table 1), and an acute JE with concomitant meningitis was diagnosed. Polymerase chain reaction (PCR) from the CSF for adenoviruses, CMV, HSV and VZV was negative, as well as reverse transcription PCR (RT-PCR) for enteroviruses, rabies virus, and JEV on March 30.

The patient slowly recovered, but there were still attention deficits and slowing of thought one month later. He also developed difficulties in swallowing which did not fully recover until he was discharged from hospital on April 12. He had not received any vaccinations against JE prior to his stay in Thailand.

2.2. Case 2

On May 9, 2011, a 54-year-old woman was seen as an outpatient in the department of tropical medicine, Medical Mission Hospital, Würzburg, Germany, with fever, lower limb ataxia and apathy after she had spent a 2 weeks holiday on the island of Bali, Indonesia. The patient had returned to Germany after a 10 h stop-over in Kuala Lumpur 9 days before in good health. During her holiday, she had visited many touristic sites on Bali and had hiked across the island. She had spent a few nights in huts together with the local population under very basic conditions. She had not sought any pre-travel advice and had not been vaccinated against any flavivirus infections. Her past medical history included a tick-borne encephalitis 15 years ago, a flavivirus infection endemic in Southern Germany. 7 days prior to the presentation at the hospital, the patient had developed high fever (40 °C) which had subsided 3 days later, shortly after the onset of a watery diarrhea. On examination, the patient presented with a second wave of fever (38.5 °C), felt extremely tired and complained of difficulties in walking straight. In addition, the right lower quadrant of the abdomen was tender to the touch. Abdominal ultrasound showed signs of diffuse hepatic damage and a partially dilated small intestine with thickening of the intestinal wall. Laboratory investigations revealed a C-reactive protein level of 0.99 mg/dl (normal <0.5 mg/dl), elevated levels of gamma-GT (46 U/l, normal <38 U/l), fibrinogen (518 mg/dl, normal <400 mg/dl), ferritin (675 ng/ml; normal <150 ng/ml), and an ESR of 54 mm/h. Procalcitonin, bilirubin, AST, ALT, LDH concentrations and kidney function tests were normal. White blood count revealed a leukocytosis of 16,500/μl, with 82% neutrophils, 7% lymphocytes and 11% monocytes. Red blood count was normal, but the platelet count was increased (508,000/μl). Thin and thick blood films for malaria were negative. A dengue fever rapid test (NADAL Dengue IgG/IgM, Nal von Minden, Germany) showed a positive IgG and negative IgM.

Clinically, JE and concomitant enteric fever was assumed. Oral ciprofloxacin 500 mg b.i.d. was commenced. However, the patient refused admission, but presented two days later to the department of neurology, Leopoldina Hospital, Schweinfurt. By then, word finding difficulties, dyslexia, dyscalculia, and a personality change were more pronounced. There was no headache, meningism, paresis or sensual deficit. Cranial nerve function and magnetic resonance imaging of the brain were normal. The EEG showed bilateral rhythmic theta- and delta-waves. CSF analysis revealed pleocytosis (22 lymphocytes/μl) with a CSF/serum albumin ratio of 23, and a CSF/serum IgG ratio of 12, diagnostic for an aseptic encephalitis. In addition, an acute perforated appendicitis was diagnosed on