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A case of aseptic meningitis due to Japanese encephalitis virus in a traveller returning from the Philippines

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Abstract

We here report the case of Japanese encephalitis virus (JEV) meningitis in a previously healthy young women returning from a trip to the Philippines. JEV is a mosquito-borne encephalitic flavivirus pathogen, which is endemic in South East and Eastern Asia. Our patient presented with aseptic meningitis and recovered well under supportive therapy. Although the chance of a traveller getting symptomatic JEV infection is extremely low, clinicians and microbiologist should be aware of patients contracting this emerging infectious disease, especially in the light of the increasing international travel.

Introduction

Japanese encephalitis virus (JEV) is a single-stranded positive sense 10-11 kb RNA virus wrapped in a nucleocapsid and surrounded by a 50 nm glycoprotein containing envelope (1, 2). It is a member of the genus *Flavivirus* in the family *Flaviviridae*, which contains many closely related human pathogens, including yellow fever virus, dengue virus and West Nile virus (3). Although JEV is the major mosquito-borne encephalitic flavivirus pathogen in South East and Eastern Asia, the actual risk for travellers to the Far East is extremely low (4). The Centres for Disease Control and Prevention concluded that the overall risk of infection with JEV for travellers to areas where JEV is endemic was < 1 case per 1.000.000 travellers (4). We here describe, to the best of our knowledge, the first confirmed case of JEV meningitis in a Belgian traveller returning from the Philippines.

Case report

A 43-year old previously healthy female patient was admitted to the emergency department of our hospital 5 days after returning from a 5-week trip to the Philippines. The trip took place in August 2009. The patient stayed in Manilla for 3 weeks, where after she visited some relatives in the rural region of Luzon. On admission, the patient appeared slightly stuporous and disoriented with fever, nausea and vomiting. Before her trip, she had not received any vaccination, nor did she take any malaria prophylaxis. Apart from evident meningismus, clinical and neurological examination revealed no abnormalities. Laboratory analysis revealed a blood CRP concentration of 5.85 mg/dl and a leucocyte count of 8.6×10^9/liter with 62% polymorphonuclear cells. Liver and kidney function were normal. Thick blood smear for malaria was negative. A Lumbar puncture was performed and revealed normal glucose, a total protein count of 136 mg/dl (normal range 12-60 mg/dl), white blood cell count of 288/mm^3 (99% mononuclear cells), and red blood cell count of 6/mm^3. On microscopy no bacteria, acid fast bacilli, or fungi were seen. Polymerase chain reaction for cocksackievirus, echovirus, herpes simplex virus and varicella zoster virus were negative. Apart from thickened meninges, MRI showed no abnormalitis. EEG showed irregular slow theta and delta waves in both hemisperes.

Because of the patient's travel history, serology for JEV, yellow fever virus, dengue virus and West Nile virus was performed in the WHO Reference and Research Centre for ARBO-viruses and Hemorrhagic Fever Viruses, Erasmus Medical Centre, Rotterdam, The Netherlands. For JEV, both IgM and IgG immunofluorescence were > 1/64. IgM for yellow fever virus, dengue virus and West Nile virus was negative, whereas IgG against these viruses was positive, probably due to cross-reaction with the JEV IgG antibodies. The patient was diagnosed with meningitis due to JEV and was admitted to the neurology department where she was treated with paracetamol. Her condition improved rapidly and

she could be discharged after 14 days of hospitalization. At follow up visit, 2 months after the acute illness, the patient's condition had further improved and was returned to her pre-illness status. Measurement of serum antibodies to JEV was repeated, and showed IgM < 1/16 and IgG > 1/64, confirming the diagnosis of an acute episode of JEV meningitis.

Discussion

Japanese encephalitis is an arthropod-borne viral infection caused by a species from the *Flavivirus* genus that occurs mainly in South and East Asia, where it is responsible for over 50,000 cases of encephalitis annually with a fatality rate in symptomatic cases of between 20 and 30% (5, 6). JEV exists in a zoonotic transmission cycle among mosquitoes, pigs, bats and water birds (1, 7). Humans become infected when bitten by an infected mosquito of the *Culex* genus (mostly *Culex tritaeniorhynchus*) and are dead-end host because of low viremia (1, 7). Areas where rice paddies are prevalent pose the greatest risk for human infection because flooded paddies are highly productive of *Culex tritaeniorhynchus* vector mosquitoes, and vertebrate amplifying hosts such as pigs and aquatic birds are collocated in these settings (8). Our patient stayed in Manila and on the Island Luzon in the months of July and August. It was shown that JEV occurs over a wide area of the Philippines with the highest transmission intensity occurring during the rainy season, which starts in June and lasts up to December (9). It was even suggested that epidemic disease is more intense in the region of Luzon compared to the area around Manila and the Southern part of the Philippines (9). Although our patient could not remember being bitten by a mosquito, we suspect that she contracted the disease while staying with her relatives in the rural area of Luzon.

The incubation period of JEV is 5-15 days (1). JEV infection is most often asymptomatic, and on average only 1 in 300 cases produce clinical symptoms (3). Symptom onset after infection with JEV occurs as a non-specific febrile illness that may include headache, cough, coryza, nausea vomiting, diarrhoea, and rigors (5). Other patients present with aseptic meningitis, poliomyelitis-like flaccid paralysis or parkinsonian syndrome (7). In severe cases, patients present with encephalitis with seizures and ultimately slip into an acute coma (7). Fatality is seen in up to 30% of the cases (10). Our patient presented with aseptic meningitis and due to her travel history, diagnosis of JEV infection could be made.

As in our patient, the typical cerebrospinal fluid findings include moderate lymphocytic pleocytosis, mild protein rise, and normal glucose (1, 11). However, because of the very low viremia, diagnosis of JEV infection is targeted towards detection of antibodies in serum and/or cerebrospinal fluid (7). The best biological diagnostic tool is the ELISA method demonstrating IgM and IgG seroconversion using 2 successive blood samples (10). Early detection of IgM in serum is a reliable indicator of JEV infection (5). Antigenic cross-reactivity among other flaviviruses such as yellow fever virus, dengue virus and West Nile virus can complicate the interpretation of serological testing. In our patient, IgM could only be detected against JEV and not against the other flaviviruses, whereas positivity for IgG against yellow fever virus, dengue virus as well as West Nile virus was probably due to cross-reactivity (10). These results, together with the biochemical profile of the cerebrospinal fluid, confirmed the diagnosis of acute meningitis due to JEV.

In the absence of specific therapy for JEV infection, intensive supportive therapy and symptomatic treatment are indicated (3, 5). As in our patient, fever should be treated using antipyretics based on paracetamol (3). In more complicated cases, parenteral nutrition, fluid and electrolyte balance monitoring, and judicious use of antibiotics are required (3). Seizures can be treated with diazepam, clonazepam, or phenytoin and abnormal movements can be treated using haloperidol (3). Corticosteroids and anti-inflammatory drugs have been investigated in the treatment of acutely infected JE patients but produced no significant beneficial effects (12). With good supportive therapy, mortality rates can be significantly reduced (12).

There are two types of JEV vaccine: JE-VAX®, a mouse brain-derived, inactivated vaccine and IXIARO®, a purified inactivated JEV vaccine that uses cell culture technology (8). Although IXIARO® contains protamine sulphate, a compound that can rarely lead to hypersensitivity reactions, it induces significantly fewer side effects compared to the licensed mouse brain-derived vaccine (8, 13). Also, post-vaccination geometric mean titers in IXIARO® recipients were significantly higher (8). IXIARO® is a vaccine registered by the European Medicine Agency (EMEA) and the only one that is commercialized in Europe (13). In Belgium, the IXIARO® vaccine can be obtained in all Belgian centres for travel medicine. The primary vaccination series consists of two separate doses of 0.5 ml given 4 weeks apart. A booster dose should be given within the second year (i.e. 12-24 months) after the recommended primary immunization (13). Vaccination is recommended for expatriates and travellers visiting endemic areas for 1 month or longer during the

transmission season and for short-term visitors (< 1 month) to rural areas who have increased risk for exposure. According to these criteria, our case patient was a candidate for pre-travel vaccination with IXIARO® (8, 14). However, our patient did not receive any pre-travel advice at all. Besides, as malaria is present in rural areas < 600 m on the island of Luzon, malaria chemoprophylaxis would have been indicated (15). As both diseases are transmitted by mosquito bites, vector control using mosquito repellent, mosquito bed nets impregnated with insecticide, clothing that covers the entire body and protects against insect bites, especially at night when *Culex tritaeniorhynchus* feeds, should have been recommended (3).

In conclusion, this is the first reported case of JEV meningitis in a Belgian patient returning from a trip to the Philippines. Although the chance of a traveller contracting symptomatic JEV infection is extremely low, clinicians and microbiologists should suspect this infection in every traveller returning from South and East Asia with an unexplained neurological syndrome.

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