Japanese encephalitis in a French traveler to Nepal

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JAPANESE ENCEPHALITIS IN A FRENCH TRAVELLER TO NEPAL

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Abstract

Japanese encephalitis is frequent in Asia, with a severe prognosis, but rare in travelers. *Culex* mosquitoes transmit Japanese encephalitis virus. Risk factors are destination, duration of stay, summer and fall seasons, outdoors activities and type of accommodation. We report the case of a French traveler to Nepal with neutralization-based serological confirmed Japanese Encephalitis. He presented classical clinical (viral syndrome before an encephalitis status with behavioral disorder, global hypotonia, mutism, movement disorders, seizure and coma), radiological (lesions of thalami, cortico-spinal tracts and brainstem) and biological features (lymphocytic meningitis). Nowadays, the presence of Japanese Encephalitis Virus in Nepal, including mountain areas is established but Japanese Encephalitis remains rare in travelers returning from this area and neurologist physicians need to become familiar with this. We recommend vaccination for travelers spending a long period of time in Nepal and having at-risk outdoor activities.

Introduction

Japanese encephalitis (JE) is an arboviral disease due to the eponymous Flavivirus (JEV) transmitted by *Culex* mosquitoes. JEV is prevalent throughout Eastern, Southern Asia and Pacific Ring Area (Misra et al, 2010). JE is one of the most frequent causes of encephalitis in the world with about 67,000 cases (incidence: 1.8/100.000) leading to 15,000 deaths annually (Campbell et al, 2011). JE leads to a severe prognosis: mortality approaches 30% of symptomatic cases and 50% of survivors present severe sequelae (Oya et al, 2007).

The risk of infection by JEV is low for travelers visiting Asia: less than one case per one million travelers (Hatz et al, 2009). This risk depends on the duration of stay, the season of travel, the practice of outdoor accommodations/activities, and the itinerary (Hills et al, 2010). No specific treatment exists, but a vaccine is available. We report a case of JE in a French traveler returning from travel in Nepal.

Case description

Our case concerns a 22-year-old man who stayed in Nepal as a volunteer for a non-governmental organization from May to September 2012. His past medical history included heavy smoking and HIV seropositivity (without immunodepression [533 CD4/mm3] and no antiretroviral therapy). Seven days after trekking in Pokhara area he presented a viral syndrome (headache, hyperthermia, asthenia) quickly followed by an agitated delirium (Day 9), then multiple seizures (Day 11) leading to coma. Routine biological tests were normal. The CD4 lymphocyte count was 892/mm^3. Cerebral tomodensitometry (CT) showed diffuse edema. Magnetic Resonance Imaging (MRI) revealed brainstem and di-encephalic lesions (thalami, cortico-spinal tracts, and corpus callosum on T2 & FLAIR sequences) without any evidence of either bleeding (T2 EG) or enhancement after gadolinium injection (fig. 2a). Cerebro-Spinal Fluid (CSF) analysis showed lymphocytic meningitis (452 cells/mm^3), slightly elevated protein rate (56 mg/dl) and normal glucose rate. Extensive plasma analyses (including serology for Hepatitis A-E viruses, Epstein-Barr virus, Rubella, Dengue virus, Measles, Chikungunya, *Treponema*, *Rickettsia* species, *Tularemia*, *Bartonella*, *Ehrlichia*, *Mycoplasma*, *Legionella*, Thick blood smear) and CSF analyses (direct exam, bacteriological, parasitological cultures and viral PCR [HSV, VZV, Measles, Toxoplasmosis, JC virus, HHV-6, Toscana virus, Mumps virus, Lymphocytic Choriomeningitis virus, Adenovirus, *Listeria*, *Cryptococcus*, Leptospirosis, *Tropheryma whipplei*, *Borrelia*]) were negative or not conclusive. Unfortunately neither plasma nor CSF pan-flavivirus PCR was available during the acute stage of the disease. After his repatriation into France, the definitive diagnosis was established by demonstrating that the serum contained neutralizing antibodies at a titre of 2,500 using the classic neutralization methods with JEV, West Nile virus, the four dengue

viruses, and Yellow fever virus. An innovative fluorescent bead-based multiplex serological assay using the Luminex xMAP method and associating up to 20 types of recombinant domain III (rEDIII) from flavivirus (Vanhomwegen and Desprès, unpublished data) confirmed the results.

Multiple antibiotics regimens (Amoxicillin, Amikacin 500mg daily, Ceftriaxone 2g daily, Meropenem, Itraconazole 100mg daily, Zithromax 500 mg daily, Acyclovir 750 mg daily, Rifampicine 600 mg daily, Isoniazide 300 mg daily, Pyrazinamide 500 mg daily, Ethambutol 1g daily) and Corticosteroid (1 mg/kg/day) had remained inefficient despite 3 weeks of treatment. The patient was repatriated from Nepal to Bangkok one week after the onset and back to France two months after the onset. He was hospitalized in our neurology department with poor clinical condition: drowsiness, mutism, quadriparesia, axial hypotonia (seated position was impossible), paroxysmal axial dystonia, and severe swallowing disorders (needing a gastrostomy). He presented multiple episodes of partial complex seizures.

Progressively he improved, and after 2 months of reeducation he was able to walk, to swallow and talk normally. He was free of seizure but he conserved a mild distal motor deficit of right upper limb and a total amnesia of the episode. Six months after the onset the patient was showing important behavioral disorders (impulsivity, intolerance to frustration, difficulties in social relationship); and one year later only mild impulsivity, moderate attention disorders and memory recall deficiency persisted. In accordance with this evolution, the MRI showed dramatic regression of lesions (Fig 1)

Discussion

JEV is transmitted between infected vertebrates through the bite of mosquitoes (mainly *Culex tritaeniorhynchus*); pigs and aquatic birds play pivotal roles as amplifying hosts. Therefore, incidence rates are much higher in rural areas, where pigs, aquatic birds and paddy-breeding vector mosquitoes are prevalent. Direct diagnosis of JE is seldom made since early clinical manifestations lack specificity. We report a case with a diagnosis of JE laboratory-confirmed by demonstration of the presence of neutralizing antibodies specific to JEV in a previously non-exposed French traveler. Our case presents classical characteristics of JE (displayed in Figure 2 and Table 1). The clinical features include an incubation period (5-15 days) followed by an aspecific viral syndrome (headache, fever), then an encephalitis syndrome (seizure, motor and sensorium deficit, movement disorders, Parkinsonism, behavioral troubles, coma). Seizures are often multiple, mostly generalized tonico-clonic and possibly leading to status epilepticus. Motor deficits are quadriplegia more than hemiplegia, upper limbs more than lower limbs, and can be due to lower or upper motor neuron lesion. Movement disorders

include tremor, chorea, focal dystonia, myoclonus and oro-facial dyskinesia. (Misra et al, 2010; Basumatary et al, 2012). Radiological explorations, based on MRI, are abnormal in 80% of cases with T2-hypersignal and T1 iso/hyposignal (topographies are resumed in Table 1). Bilateral thalami lesions are highly evocative. (Kalita et al, 2000). CSF analyses are abnormal in more than 80% of cases. The clinical course consists of an acute short-lived illness and a prolonged convalescence.

Imported cases of JE remain rare but their incidence has been increasing for the last three decades (Hills et al, 2010; Buhl and Lindquist 2009). Whereas JE mostly concerns the pediatric population in endemics areas, residents of all ages of developed countries have no immunity to JEV and are susceptible to severe infection. However, short-term tourism has not been associated with a significant risk for contracting JE. The Katmandu Valley is now well-known for endemic transmission of JEV (Thakkur et al, 2012; Impoinvil et al, 2011; Bhattachan et al, 2009; Partridge et al, 2007). For travelers to rural areas where JE is endemic, the estimated risk for JE during the transmission period is 1 per 20,000 per week (Halstead & Tsai 2004). Because of the availability of a vaccine, the nature of the stay of this patient was in adequation with immunization recommendations (long stay, endemic geographic area, HIV+, outdoor professional and leisure activities, travel itinerary including rural areas) (Burchard et al 2009).

Conclusion

This case of JE in a French traveler returning from Nepal reemphasizes the need to disseminate revised recommendations on travel vaccines towards general practitioners and the general population. In the context of the recent increase in incidence of imported JE cases (Buhl and Lindquist 2009, Tappe et al 2012, Werlinrud et al 2011), it is crucial for neurologists to be aware of the possibility of JE in their at-risk population. They also must become familiar with the epidemiological, clinical and paraclinical features consistent with the diagnosis of JE.

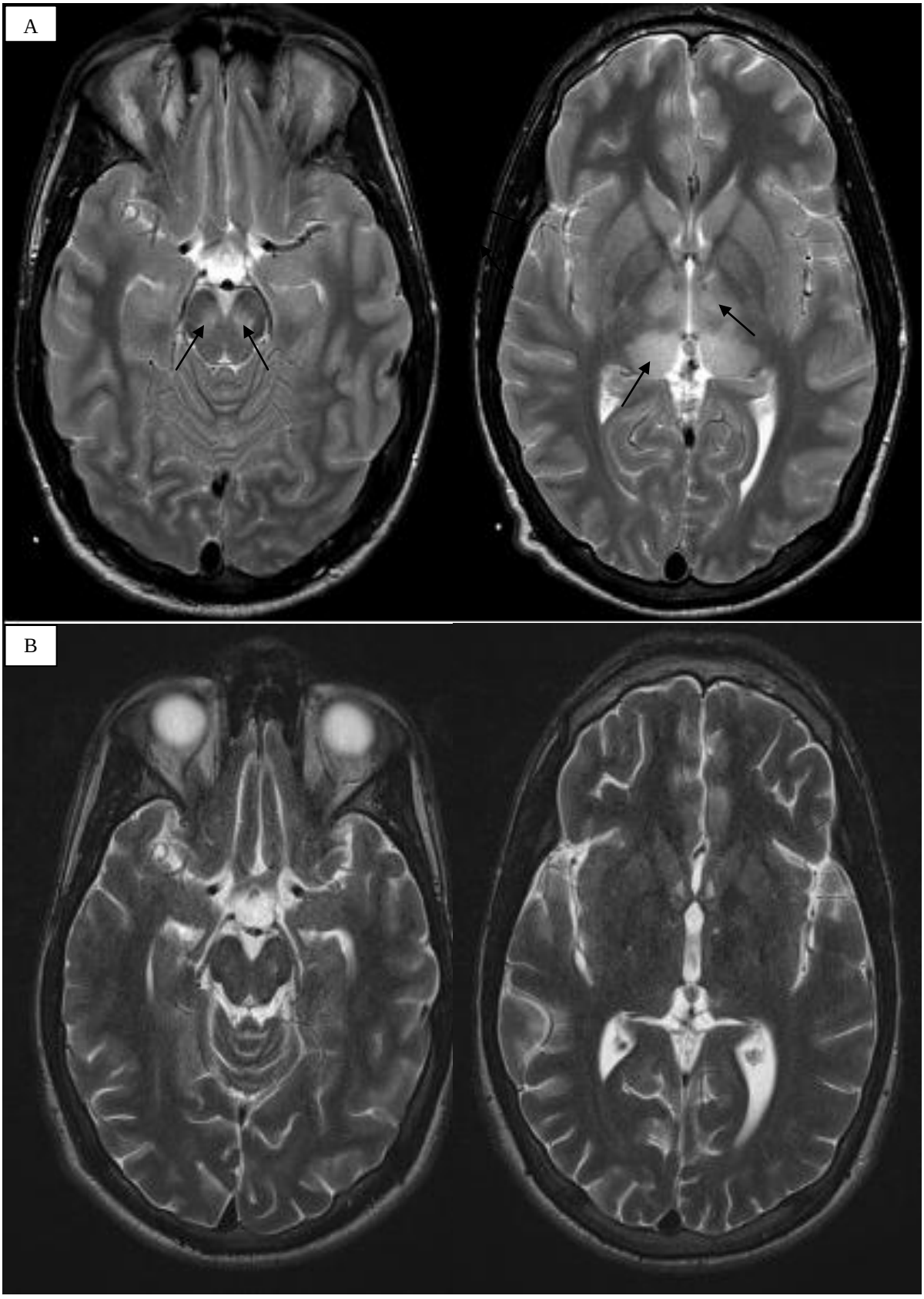

Figure 1: T2 sequences of cerebral MRI 15 days (A) and 5 month (B) after the onset.

A: lesion of thalami, brainstem and cortico-spinal tracts

B: dramatic regression of lesion after 5 month

Figure 2: JE Clinical Features

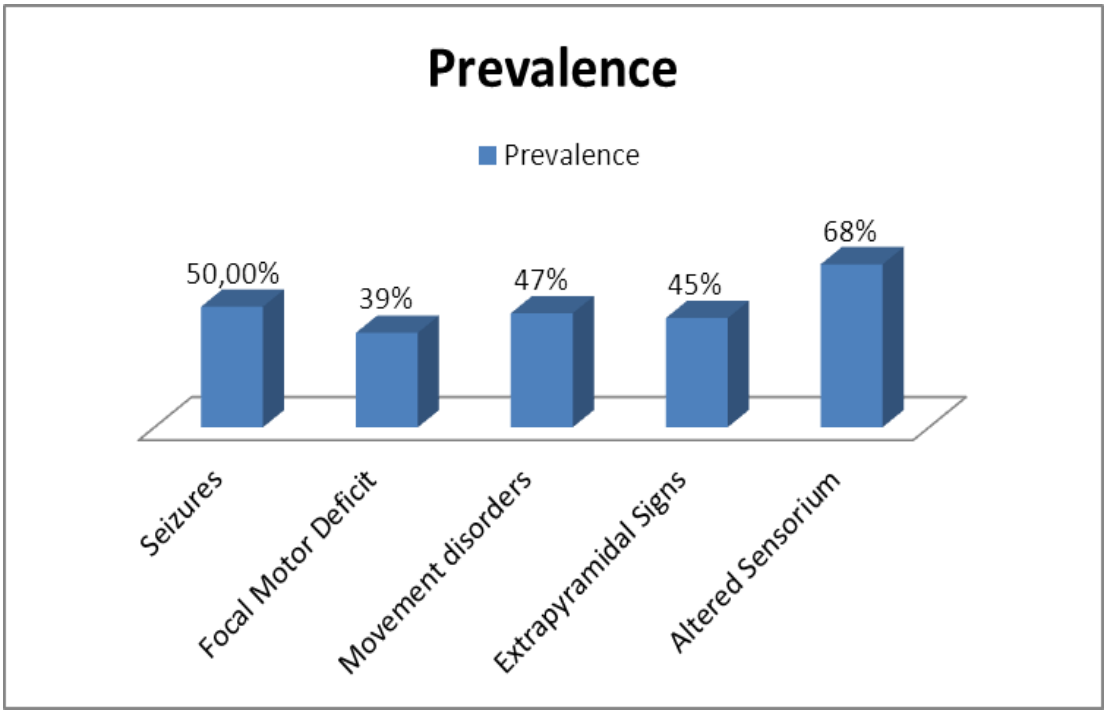

Table 1: JE CSF Analysis, MRI and EEG Features

CSF Analysis *(Median value)*	MRI Lesions *(Prevalence)*	EEG
✓ Mild Protein rates elevation *(70mg/dl)* ✓ Pleiocytosis *(66,5/mm3)* ✓ Lymphocytic predominance	✓ Thalami *(94%)* ✓ Midbrain *(58 %)* ✓ Basal ganglia *(38,5%)* ✓ Cerebellum *(25.8%* ✓ Pons *(19%)* ✓ Cortex *(19%)*	✓ Diffuse background activity slowing ✓ Spike-Wave discharges

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