

Is Japanese encephalitis virus the aetiology in patients with anti-JEV IgM in cerebrospinal fluid?

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Acute encephalitis is an important cause of death and morbidity in Asia, especially in children. Japanese Encephalitis virus (JEV) is reported as the most commonly identified infectious aetiology. JEV is an arbovirus transmitted between *Culex* mosquitoes, pigs, water birds and humans.¹ Tsai and colleagues estimated 175,000 cases (43,750 deaths) due to JEV in 1994.² The epidemiological situation remains unclear with high inequity from country to country in term of JEV vaccination and reporting.³ The recommended diagnostic methods are viral isolation, RT-PCR, or detection of anti-JEV IgM antibody preferentially in CSF, or in serum.⁴ However, because of transient, early viraemia, direct detection has apparent low sensitivity.⁵

We recruited, between 2003 and 2011, 131 patients admitted with acute encephalitis syndromes (AES, including meningo-encephalitis presentations, 107 patients) or pure meningitis syndromes (24 patients) at Mahosot Hospital, Vientiane, Lao PDR, who fulfilled the WHO criteria for biologically confirmed JEV. Diagnosis relied on direct viral detection in CSF (5 patients, 4%) and detection of anti-JEV IgM (126 patients, 96%) in CSF (71%) or just sera (25%) (table 1).

In patients with a serological diagnosis of JEV, we identified alternative aetiologies in 15%, using direct diagnosis (*i.e.* PCR or pathogen isolation). Many of the pathogens detected have been associated with neurological infections and constitute convincing aetiologies that alone could explain the patients' clinical presentation. We cannot rule out that this series includes actual dual infections since JEV may share exposure risk factors with other pathogens. However, our results suggest that the diagnosis of JEV infection by serology may be inaccurate in a significant proportion of patients.

If this hypothesis is correct, the Positive Predictive Value of anti-JEV IgM detection would appear to be low; lowest in patients with meningitis and when IgM is detected only in serum (alternative aetiologies identified in 12% of patients with AES; 29% with meningitis; 13% with CSF anti-JEV IgM; 21% with blood anti-JEV IgM only). Diagnosis of JEV infection by IgM detection may be faulted by antigenic cross-reaction and by actual secretion of anti-JEV IgM during another neurological infection in patients previously immunised against JEV.

As JEV is a significant public health burden in Asia, this observation deserves attention. It suggests that the incidence of acute neurological infections due to JEV may be overestimated and that detection of anti-JEV IgM in such patients should not preclude the management of other treatable aetiologies, in particular bacterial infections. Research for improvement of JEV diagnosis is needed.

References

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- 3 Tarantola A, Goutard F, Newton P, *et al.*. Estimating the Burden of Japanese Encephalitis Virus and Other Encephalitides in Countries of the Mekong Region. *PLoS Negl Trop Dis* 2014; **8**: e2533.
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Conflicts of interest

All authors declare no conflict of interest.

Table 1. Alternative aetiologies detected in JEV patients with acute encephalitis or meningitis syndrome.

	Acute Encephalitis Syndrome* (107 patients)			Pure Meningitis** (24 patients)	
	JEV detection in CSF (PCR or culture)	Anti-JEV IgM detection in CSF	Anti-JEV IgM detection in blood only	Anti-JEV IgM detection in CSF	Anti-JEV IgM detection in blood only
Number of patients	5 [§]	77	25	16	8
Number of patients with an alternative aetiology (detection in CSF by culture or PCR)	0	5 (9%)	2 (1%)	5 (31%)	2 (25%)
List of pathogens detected		+ <i>Leptospira</i> sp. (1) + <i>Mycobacterium tuberculosis</i> (1) + <i>Streptococcus pneumoniae</i> (2) + <i>Cryptococcus neoformans</i> var <i>grubii</i> (1)	+ <i>Rickettsia typhi</i> (1) + <i>Streptococcus pneumoniae</i> (1)	+ <i>Orientia tsutsugamushi</i> (3) + <i>Cryptococcus neoformans</i> var <i>grubii</i> (1) + <i>Cryptococcus</i> sp. (1)	+ <i>Orientia tsutsugamushi</i> (1) + <i>Varicella zoster virus</i> (1)
Number of patients with an alternative aetiology (detection in blood by culture or PCR)	0	2 (3%)	3 (1%)	0	0
List of pathogens detected		+ <i>Rickettsia typhi</i> (1) + Dengue virus (1)	+ <i>Burkholderia pseudomallei</i> (2) + <i>Orientia tsutsugamushi</i> (1)		

* AES patient is a person of any age, at any time of year with acute onset of fever and either a change in mental status and/or new onset of seizures (excluding simple febrile seizures, defined as a seizure that occurs in a child aged 6 months to less than 6 years old, whose only finding is fever and a single generalized convulsion lasting less than 15 minutes, and who recovers consciousness within 60 minutes of the seizure).

** Pure meningitis is defined as a sudden onset of fever with neck stiffness.

§ anti-JEV IgM was detected in CSF for two patients.

All CSF and serum samples were tested using the Panbio JEV/Dengue IgM Combo ELISA kit (Alere), WHO-recommended test for JEV diagnosis.