

# Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis

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## Summary

Japanese encephalitis (JE) causes at least 10 000 deaths each year. Death is presumed to result from infection, dysfunction and destruction of neurons. There is no antiviral treatment. Seizures and raised intracranial pressure (ICP) are potentially treatable complications, but their importance in the pathophysiology of JE is unknown. Between 1994 and 1997 we prospectively studied patients with suspected CNS infections referred to an infectious disease referral hospital in Ho Chi Minh City, Vietnam. We diagnosed Japanese encephalitis virus (JEV), using antibody detection, culture of serum and CSF, and immunohistochemistry of autopsy material. We observed patients for seizures and clinical signs of brainstem herniation, measured CSF opening pressures (OP) and, on a subset of patients, performed EEGs. Of 555 patients with suspected CNS infections, 144 (26%) were infected with JEV (134 children and 10 adults). Seventeen (12%) patients died and 33 (23%) had severe sequelae. Of the 40 patients with witnessed seizures, 24 (62%) died or had severe sequelae, compared with 26 (14%) of 104 with no witnessed seizures [odds ratio (OR) 4.50, 95% confidence interval (CI) 1.94–10.52,  $P < 0.0001$ ]. Patients in status epilepticus ( $n = 25$ ),

including 15 with subtle motor seizures, were more likely to die than those with other seizures ( $P = 0.003$ ). Patients with seizures were more likely to have an elevated CSF OP ( $P = 0.033$ ) and to develop brainstem signs compatible with herniation syndromes ( $P < 0.0001$ ). Of 11 patients with CSF OP  $\geq 25$  cm, five (46%) died, compared with seven (9%) of 80 patients with lower pressures [OR 8.69, 95% CI 1.73–45.39,  $P = 0.005$ ]. Of the 50 patients with a poor outcome, 35 (70%) had signs compatible with herniation syndromes (including 19 with signs of rostro-caudal progression), compared with nine (10%) of those with better outcomes ( $P < 0.0001$ ). Of 11 patients with CSF OP  $\geq 25$  cm, five (46%) died, compared with seven (9%) of 80 patients with lower pressures (OR 8.69, 95% CI 1.73–45.39,  $P = 0.005$ ). The combination of coma, multiple seizures, brainstem signs and illness for 7 or more days was an accurate predictor of outcome, correctly identifying 42 (84%) of 50 patients with a poor outcome and 82 (87%) of 94 with a better outcome. These findings suggest that in JE, seizures and raised ICP may be important causes of death. The outcome may be improved by measures aimed at controlling these secondary complications.

**Keywords:** brainstem herniation; flavivirus; outcome; status epilepticus

**Abbreviations:** ICP = intracranial pressure; IgG = immunoglobulin G; IgM = immunoglobulin M; JE = Japanese encephalitis; JEV = Japanese encephalitis virus; LP = lumbar puncture; OP = opening pressure

## Introduction

Japanese encephalitis (JE) is the most important epidemic viral encephalitis in the world, with an estimated 50 000 cases annually (Advisory Committee on Immunization Practices, 1993). Approximately 30% of patients die, and half the survivors are left with severe neurological sequelae (Hoke *et al.*, 1988; Solomon *et al.*, 2000a). The disease is caused by an enzootic flavivirus—Japanese encephalitis virus (JEV)—which is transmitted between pigs, chickens and other animals by *Culex* mosquitoes. Humans become infected when living or travelling in close proximity to this enzootic cycle. JEV is mostly confined to Asia, but related neurotropic flaviviruses, including West Nile virus, Murray Valley encephalitis virus and Tick-borne encephalitis virus, occur elsewhere and cause similar diseases (Tsai, 1997; Kaiser, 1999; Solomon and Cardoso, 2000). JEV is neurotropic, and after crossing the blood–brain barrier replicates rapidly in neurones, prompting a perivascular inflammatory reaction (Johnson *et al.*, 1985). Infection, dysfunction and subsequent destruction of neurones are presumed to be the main cause of death in JE (Innis, 1995). The importance of potentially treatable secondary complications, such as seizures, raised intracranial pressure (ICP) and brainstem herniation, has not been assessed. We report here observations on 144 patients infected with JEV, who were investigated during prospective clinical studies of CNS infections in Vietnam.

## Patients and methods

The studies were conducted over 3 years from January 1995 at the paediatric and adult intensive care units at the Center for Tropical Diseases, Ho Chi Minh City, an infectious diseases referral hospital for much of southern Vietnam, where JEV is endemic. Study protocols were approved by the hospital's scientific and ethical committee, and consent was obtained from the patient or accompanying relative. Adults and children (age <15 years) with suspected CNS infections were studied. CNS infections were suspected in patients with a fever, or history of fever, and at least one of the following: reduced level of consciousness [Glasgow coma score <14 (Teasdale and Jennett, 1974), or for children <6 years, Blantyre coma score <4 (Molyneux *et al.*, 1989)]; severe headache; neck stiffness; tense fontanelle; focal neurological signs; or seizures. Children between 6 months and 5 years of age with a single convulsion lasting <15 min who recovered consciousness within 60 min were considered to have had a simple febrile convulsion (Verity *et al.*, 1985) and were not studied. Patients with slide-positive cerebral malaria or clinical features of tetanus were admitted to specialized wards and thus not included in the series.

A detailed history was taken, and a clinical examination, including full neurological examination, was performed daily or more frequently as indicated, by a member of the study team until death or discharge. Clinical data were analysed subsequently for combinations of clinical signs compatible

with uncal or central cerebral herniation syndromes (Table 1) (Plum and Posner, 1982; Newton *et al.*, 1991).

The minimum criteria required to define a herniation syndrome were as described by Newton and colleagues, except that pupillary dilatation was not assessed in patients whose pupils had been dilated to allow fundoscopy (Newton *et al.*, 1991). Recorded herniation data were later reviewed independently by one of us (F.J.K.) and where there was disagreement a consensus was reached. Status epilepticus was defined as a series of motor seizures, generalized, unilateral or partial, without recovery of consciousness between fits, or a single prolonged convulsion of >30 min (Aicardi and Chevrie, 1983). On admission, a lumbar puncture (LP) was performed in the left lateral position and, if the patient was calm, opening pressures (OP) were measured with a spinal fluid manometer. LP was delayed in convulsing patients or in those with clinical signs of raised ICP. If a patient died before LP, CSF was taken immediately post-mortem for diagnostic purposes. Blood pressure was measured with a sphygmomanometer, and cerebral perfusion pressure was calculated (Waller *et al.*, 1991). CSF was examined for cell count and differential, protein, glucose, lactate, Gram stain, bacterial and viral culture. Blood was taken for haematocrit, examination for malarial parasites, platelet count, differential white cell count, blood cultures, glucose, lactate, biochemical screen, viral culture and serology. In the event of a patient death, permission was sought for full autopsy, or post-mortem needle biopsy via the foramen magnum. There were no on-site facilities for acute CT or MRI scanning. Prolonged or repeated seizures were treated with diazepam (0.25 mg/kg), followed if necessary by intravenous (i.v.) phenobarbitone (10 mg/kg), but there were no facilities for paralysing and electively ventilating patients in status epilepticus. Mannitol (0.5–1 g/kg) was given to patients with elevated CSF OP or clinical signs of raised ICP. Suspected septicaemia was treated with broad-spectrum antibiotics. During the second half of the study period, children with encephalitis were treated with either interferon alpha (Roferon) 10 MU/m<sup>2</sup>/day for 7 days or placebo as part of a randomized double-blind trial. At discharge, patients' outcomes were classified using criteria modified from those of Whitley (Table 2) (Whitley *et al.*, 1986): 1 = died; 2 = severe sequelae, incompatible with independent living; 3 = moderate sequelae, affecting function, but compatible with independence; 4 = minor sequelae including altered personality or clinical signs not affecting function; 5 = full recovery.

## Electrophysiological studies

From April 1996, EEG recordings were made on patients with encephalitis, using a 14 channel Microscribe 180TM (SLE, Surrey, UK) and silver/silver chloride electrodes placed according to the International 10–20 system. Recordings were made as soon after admission as possible, at 12 and 24 h,

**Table 1** Possible herniation syndromes in patients with Japanese encephalitis\*

	Better outcome (n = 94)	Poor outcome (n = 50)	Odds ratio (95% CI)	P value
Uncal	0	1	ND	0.347
Unilateral dilated pupil				
Unilateral ptosis				
Oculocephalic and/or oculovestibular minimal deviation				
Hemiparesis				
Diencephalic	3	7	4.72 (1.03–24.42)	0.035
Cheyne-Stokes respiration				
Small or midpoint pupils reactive to light				
Oculocephalic and/or oculovestibular full deviation				
Flexor response to pain and/or decorticate posturing				
Hypertonia and/or hypereflexia with extensor plantars				
Midbrain/upper pontine	5	7	2.77 (0.73–10.79)	0.116
Hyperventilation				
Midpoint pupils, fixed to light				
Oculocephalic and/or oculovestibular minimal deviation				
Extensor response to pain and/or decerebrate posturing				
Lower pontine	0	10	ND	<0.0001
Shallow or ataxic respiration				
Midpoint pupils, fixed to light				
Oculocephalic and/or oculovestibular no response				
Flexion legs only or no response to pain				
Flaccidity with extensor plantars				
Medullary	0	11	ND	<0.0001
Slow irregular or gasping respiration				
Pupils dilated and fixed to light				
Respiratory arrest with adequate cardiac output				
Any herniation syndrome	9	35	21 (7.73–59.02)	<0.0001
Rostro-caudal progression	0	19	ND	<0.0001

\*If more than one syndrome documented, worst is shown; three patients were documented progressing through three levels of herniation. ND = not determined.

**Table 2** Outcome of 144 patients infected with Japanese encephalitis virus

Outcome grade <sup>#</sup>	No. (%) of patients
1. Died	17 (12)
2. Severe sequelae	33 (23)
Severe cognitive impairment with spastic quadraparesis (22)	
Severe cognitive impairment with hemiparesis (5)	
Severe cognitive impairment with no gross motor abnormality (4)	
Mentally normal, but bed bound due to gross motor deficits affecting all limbs (2)*	
3. Moderate sequelae	39 (27)
Diplegia (12 flaccid, 4 spastic, 2 with urinary sphincter problems) (16)	
Hemiparesis (3 with mild cognitive impairment, 1 with tremor, 1 with UMN CN VII) (14)	
Monoplegia (4 flaccid, 1 spastic) (5)	
Extrapyramidal syndromes (2 with tremors, 1 opisthotonus, 1 ataxia) (4)	
4. Minor sequelae	27 (19)
Altered personality (2 with mild intention tremor) (7)	
Frontal release signs (2)	
Upper motor neurone signs (extensor plantars, clonus, brisk reflexes) (16)	
Slight intention tremor (2)	
5. Full recovery	28 (19)

<sup>#</sup>Number of patients in parentheses.

\*Spastic arms and right leg, flaccid left leg in one patient; gross flaccid paralysis of all limbs and trunk in one patient.

**Table 3** Background acute EEG grade for 55 patients with Japanese encephalitis\*

	Better outcome (n = 34)	Poor outcome† (n = 21)	Odds ratio (95% CI)	P value
Normal	1	0	ND	1.000
Ia Moderate or large amplitude slow waves, reactive	27	8	0.16 (0.04–0.62)	0.005
Ib Moderate or large amplitude slow waves, unreactive	4	5	2.34 (0.45–12.49)	0.279
II Low amplitude (<50 µV)	0	1	ND	0.382
IIIa Burst suppression	0	1	ND	0.382
IIIb Isoelectric	0	0	ND	ND

\*Modified from Tasker *et al.*, 1988. For patients with serial acute EEGs the worst grade is given. †The poor outcome group included eight patients that died. ND = not determined.

discharge, follow-up, and at additional times as indicated clinically. Unusual neurological signs, including subtle motor seizures, were recorded on video. EEGs were analysed by one of us (S.S.) who knew the age of each child, but was blind to other clinical information. The background electrical activity on acute EEGs was graded according to the criteria in Table 3, modified from Tasker (Tasker *et al.*, 1988).

### Virological and serological studies

Anti-JEV immunoglobulin M (IgM) antibodies were evaluated in acute and convalescent sera and CSF using a rapid IgM dot enzyme immunoassay which distinguishes antibodies to JEV and dengue (Solomon *et al.*, 1998b). IgM and immunoglobulin G (IgG) titres were measured subsequently using a double sandwich capture ELISA (enzyme-linked immunosorbent assay) (Innis *et al.*, 1989). For serum 40 units of IgM to JEV (with JEV IgM greater than dengue IgM), or for paired samples a rise from <15 to >30 units was considered evidence of acute JEV infection (Innis *et al.*, 1989). An IgM : IgG ratio greater than 1.8 : 1 was considered evidence for a primary flavivirus infection, whilst a ratio <1.8 was considered evidence that the patient had previously been infected with a different flavivirus (secondary infection) (Innis *et al.*, 1989). These assays, which have high sensitivity and specificity after the first few days of illness, have become the accepted standard for diagnosing JE (Innis, 1995; Solomon *et al.*, 2000a). Autopsy material, and acute serum and CSF samples were inoculated into *Aedes albopictus* C6/36 cells, rhesus monkey kidney (LLC-MK2) cells, and Vero cells for isolation of JEV or other viruses (Solomon *et al.*, 1998a; Solomon *et al.*, 2000b). Four micron formalin-fixed paraffin sections of autopsy material were stained with streptavidin alkaline phosphatase using JEV polyclonal mouse ascitic fluid to demonstrate JEV antigen immunohistochemically (Myint *et al.*, 1999).

### Statistical analysis

Normally distributed data were compared using student's *t*-test; data that were not normally distributed were compared by the Mann–Whitney *U* test. Cut-off values for continuous

data were based upon standard indices and decided before the analysis. Differences between proportions were tested using the  $\chi^2$  test with Yates' correction or Fisher's exact test (Statview 4.02; Abacus Concepts Inc.). Variables associated with a poor outcome in univariate analyses were included in a stepwise logistic regression to create a model predictive of a poor outcome (SPSS version 9). Terms were entered into the model and remained in only if they were statistically associated with a poor outcome ( $P < 0.05$ ). Both forward selection and backward elimination methods were used. Based on the results of this logistic regression the sensitivity, specificity and positive and negative predictive values of the model were tested.

### Results

During the 3-year study, 555 patients with suspected CNS infections were investigated: 134 (45%) of 296 children, and 10 (4%) of 239 adults were infected with JEV. Other patients have been described previously (Solomon *et al.*, 1998a; Solomon *et al.*, 2000b). Diagnosis was based on elevated anti-JEV IgM in the serum and CSF of 99 patients, serum alone of 44 patients, and positive immunohistochemistry of post-mortem brain tissue of one patient. JEV was isolated from the CSF of one patient, who died, with antibody in CSF and serum. In 107 patients the infection was primary, in 36 secondary, and in one patient it was not classified. Primary infections occurred in 39 (90%) of 43 children under 6 years, compared with 68 (69%) of 100 patients over 6 years [odds ratio (OR) 4.59, 95% confidence interval (CI) 1.40–16.58,  $P = 0.008$ ], but there was no relationship between age or classification of infection and outcome. Overall, 27 patients had a negative admission serum sample and seroconverted in hospital. Seventeen patients (12%) died (16 children), between 4 h and 272 days after admission (median 74 h); 33 patients (23%) had severe, 39 (27%) moderate, and 27 (19%) minor neurological sequelae (Table 2). Only 28 patients (19%) made a full recovery. Of those with moderate sequelae, five could walk normally, 11 walked independently but abnormally, six walked with help, and 17 could not walk at all. The median (range) time to a full coma score was 5 (1–42) days. For the purposes of analysis, patients who died or

**Table 4** Features in the history [no. (%)] of 144 patients infected with Japanese encephalitis virus

	Better outcome (n = 94)	Poor outcome (n = 50)	Odds ratio (95% CI)	P value
Males	56 (60)	26 (52)	0.74 (0.35–1.55)	0.486
Age in years [median (range)]	8 (1.67–75)	7 (1.58–18)	ND	0.256
From rural location	74 (79)	47 (94)	4.23 (1.10–19.01)	0.032
Length of illness (days) [median (range)]	5 (2–14)	6 (3–26)	ND	0.062
Headache	63 (67)	34 (68)	0.91 (0.41–2.95)	0.956
History of convulsions	35 (37)	24 (48)	1.45 (0.68–3.09)	0.386
More than one convulsion in history	17 (18)	19 (38)	2.63 (1.13–6.17)	0.023
History of spasms	12 (13)	15 (30)	2.79 (1.09–7.16)	0.030
History of neck stiffness	55 (59)	17 (34)	0.33 (0.15–0.72)	0.004

ND = not determined; numbers in parentheses are percentages.

**Table 5** Initial examination findings [no. (%)] of 144 patients infected with Japanese encephalitis virus

	Better outcome (n = 94)	Poor outcome (n = 50)	Odds ratio (95% CI)	P value
Pulse [median (range) beats per minute]	120 (60–180)	120 (80–140)	ND	0.065
Respiration rate [median (range) breaths per minute]	25 (20–48)	32 (20–52)	ND	0.0003
Coma*	41 (44)	42 (84)	6.27 (2.48–16.38)	<0.0001
Able to localize pain	69 (73)	16 (32)	0.17 (0.07–0.38)	<0.0001
Seizure now	8 (9)	9 (18)	2.25 (0.73–7.01)	0.19
Rigidity spasms on examination	10 (11)	22 (44)	6.29 (2.46–16.37)	<0.0001
Facial nerve palsy	12 (13)	7 (14)	1.06 (0.35–3.17)	0.883
Hemiparesis	14 (15)	9 (18)	1.19 (0.43–3.26)	0.892
Decerebrate/decorticate posturing	10 (11)	27 (54)	9.39 (3.68–24.49)	<0.0001
Opisthotonus	5 (5)	12 (24)	5.37 (1.6–18.98)	0.003
Increased limb tone	23 (25)	32 (64)	5.18 (2.31–11.76)	<0.0001
Clonus	7 (7)	10 (20)	2.96 (0.95–9.44)	0.064
Absent abdominal reflex	64 (68)	46 (92)	4.67 (1.42–17.02)	0.008
CSF OP [median cm CSF (range)]**	15.3 (7–31)	18.0 (6–32)	ND	0.163

\*Glasgow coma score <11 or, for children <6 years old, Blantyre coma score <4.

\*\*OP was measured for 33 (76%) patients in the poor outcome and 58 (62%) in the good outcome group.

Numbers in parentheses are percentages.

had severe sequelae were defined as the poor outcome group; those with full recovery, moderate or minor sequelae were the better outcome group.

### Admission clinical features

Patients typically presented with fever, headache and vomiting followed by confusion and coma, often heralded by a seizure (Table 4).

One hundred and four patients (74%) were admitted with impaired consciousness. Thirty-seven were fully conscious on admission: 13 with meningism (including two with seizures before admission, and one with a third cranial nerve palsy); 18 with acute flaccid paralysis; and six with a hemiparesis. Of these patients, 15 (10 flaccid paralysis, five hemiparesis) subsequently developed encephalitis 6–48 h after admission. A history of rigidity spasms was more common in patients with a poor prognosis, whilst nuchal rigidity was less common (Table 4). On initial examination, coma, inability to localize pain, tachypnoea, decerebrate/decorticate posturing, abnormal oculocephalic reflexes,

absent abdominal reflexes, increased limb tone and opisthotonus were all associated with a poor prognosis (Table 5).

### Seizures

A history of seizures was reported in 59 patients (41%) (38 children). Of the 36 patients with more than one seizure in the history, 19 (53%) had a poor outcome, compared with 31 (29%) of 108 with a single or no seizures (OR 2.78, 95% CI 1.19–6.49,  $P = 0.015$ ). Seventeen children had seizures during the initial examination and 40 had witnessed seizures at some time during the admission. Of these, 24 (62%) had a poor outcome compared with 26 (14%) of 104 with no witnessed seizures (OR 4.50, 95% CI 1.94–10.52,  $P < 0.0001$ ). Witnessed seizures were more common in children <6 years old [18 (42%) of 43 patients versus 22 (22%) of 101 patients; OR 2.59, 95% CI 1.12–5.99,  $P = 0.024$ ]. Of the 29 patients with more than one witnessed seizure, 21 (72%) had a poor outcome compared with four (33%) of 12 with a single seizure (OR 5.25, 95% CI 1.02–29.38,  $P = 0.024$ ). Seven children had partial motor seizures, 18 had generalized tonic

clonic seizures and 15 had seizures with subtle clinical manifestations: five of these had intermittent minimal clonic movements (twitching) of a digit, eyebrow, eyelid or mouth; eight had twitching plus nystagmus, eye deviation, excess salivation or irregular breathing; one had just nystagmus and excess salivation; and one had just tonic eye deviation. Ten of the patients with generalized tonic clonic seizures and all of those with subtle seizures were in status epilepticus. Patients in status were more likely to die than those with other seizures [11 (44%) of 25 versus none of 15;  $P = 0.003$ ]. There was no relationship between seizures and core temperature or blood glucose concentration.

### EEG findings

Two hundred and thirty-four EEGs were performed on 55 patients; 126 acutely, 52 during convalescence and 56 at follow up. The median (range) number of EEGs per patient was four (1–11). The relationship between background EEG grade and outcome is shown in Table 3. Sixteen (84%) of 19 patients with grade 1b or worse had poor outcome, compared with 14 (39%) of 36 with less severe grades (OR 8.38, 95% CI 1.79–44.55,  $P = 0.003$ ). There were asymmetrical patterns in 15 patients, but these were unrelated to outcome. Seizures were documented in the acute EEGs of 11 (20%) patients: isolated discharges in the frontal lobe of two patients; periodic lateralized epileptiform discharges in the right hemisphere of one patient with generalized tonic clonic seizures; multiple seizures in two patients; and continuous discharges in six patients, three of whom also had periodic lateralized epileptiform discharges. In one patient, electrical status epilepticus was manifested clinically by generalized tonic clonic seizures; in the remaining seven with multiple or continuous seizures, the clinical signs were subtle, as described above. Continuous seizures were localized to frontal, fronto-central, parieto-occipital and parieto-temporal areas. Six (55%) of 11 patients with seizures on EEG died, compared with four (9%) of 44 with no recorded seizures (OR 12.00, 95% CI 2.01–80.62,  $P = 0.002$ ).

During convalescence, 52 EEGs were performed on 38 patients: 14 had normal EEGs; 20 had mildly slow but reactive EEGs; two patients with severe neurological sequelae had large amplitude slow waves and no reactivity; one patient had burst suppression and one had an isoelectric pattern—both of these patients subsequently died. EEGs were repeated in 36 patients at follow-up 3–12 months after the illness onset: 27 were normal, seven were mildly slow, and two remained severely abnormal.

### Movement disorders

Other movement disorders were common, occurring in 38 patients: 27 had intermittent resting tremors (10 generalized, 17 localized), exacerbated by stimulation, particularly pain; 12 patients had orofacial dyskinesias (lip-smacking/chewing, bruxism, grimacing); four had choreoathetosis; two had

mandibular dystonias; one had hiccups; and one had opsoclonus myoclonus. Six patients had cogwheel rigidity. There was no relationship between these movement disorders and outcome.

### Investigations

CSF OP was measured reliably in 91 patients (63%) (Table 5). Thirty (52%) of 58 patients with a good outcome, and 18 (55%) of 33 with a poor outcome had OP above normal for age ( $P = 0.97$ ). Of the 30 patients with a seizure in the previous 24 h, 13 (43%) had an OP  $\geq 20$  cm CSF, compared with 12 (20%) of 61 who did not (OR 3.12, 95% CI 1.08–9.12,  $P = 0.033$ ). Of the 11 patients with OP  $\geq 25$  cm CSF, five (46%) died, compared with seven (9%) of 80 with lower pressures (OR 8.69, 95% CI 1.73–45.39,  $P = 0.005$ ). Median (range) cerebral perfusion pressure was 78.8 (59.5–100.2) mmHg, but did not relate to outcome. No patient had a cerebral perfusion pressure  $< 40$  mmHg. One hundred and twelve patients had CSF pleocytosis ( $> 4$  white blood cells/ml; median 53, range 0–559), 64 had lymphocyte and 27 had neutrophil predominance. The median (range) CSF protein was 62 (13–168) mg%, and the mean (standard deviation) CSF/plasma glucose ratio was 61.9% (14.6). There were no differences between outcome groups in these parameters. CSF lactates were higher in those with poor outcome [median lactate 2.65 mmol/l (range 1.4–8.7) versus 2.4 mmol/l (0.3–5.3),  $P = 0.064$ ]. The CSF lactate/glucose ratio was higher in patients with seizures in the previous 12 h [median 0.89 (range 0.34–4.7) versus 0.65 (range 0.09–1.91),  $P = 0.048$ ]. Forty-nine patients (34%) had a peripheral leucocytosis [mean WCC 13.1 (5.7 SD)  $\times 10^9/l$ ], with a predominance of neutrophils in 130 (90%), but there was no difference between outcome groups. Seven of the poor and 15 of the better outcome group had sodium  $< 135$  mmol/l, but only five patients (two poor outcome, three better outcome) had sodium  $< 130$  mmol/l. No patient had hypoglycaemia.

### Possible herniation syndromes

One patient had signs compatible with uncal herniation, 45 (31%) had signs compatible with central brainstem herniation syndromes, and 19 (14%) had clinical deterioration consistent with rostro-caudal progression (Table 1). Herniation syndromes and rostro-caudal progression were significantly associated with poor outcome. Three patients were documented progressing through three levels of central herniation. A 14-year-old boy who had progressed from a diencephalic to a lower pontine syndrome was treated with mannitol and hyperventilation by bag and mask; he regained spontaneous respirations and normal oculocephalic and pupillary reflexes, before deteriorating to a medullary syndrome and eventually dying. An 8-year-old boy deteriorated from a diencephalic to a midbrain-upper pontine syndrome, and improved following mannitol, regaining oculocephalic responses; he subsequently deteriorated to a lower pontine syndrome and died. Another

**Table 6** Multiple logistic regression analysis of the factors associated with poor outcome in Japanese encephalitis\*

Variable	Adjusted OR (95% CI)	P value
Coma**	5.87 (1.84–18.67)	0.003
More than one witnessed convulsion	6.30 (1.52–26.04)	0.011
Herniation syndrome	32.35 (9.07–115.41)	<0.001
Ill for 7 days or more	13.00 (3.51–48.23)	<0.001

\*Terms were entered into the model and remained in only if they were statistically associated with a poor outcome ( $P < 0.05$ ). \*\*Glasgow coma score <11 or, for children <6 years old, Blantyre comas score <4.

8-year-old boy deteriorated from a diencephalic to a lower pontine syndrome after an episode of status epilepticus; following treatment with diazepam, phenobarbitone and mannitol he improved, regaining normal eye movements and withdrawal from pain; however, he deteriorated again, developing a medullary syndrome before dying. Herniation syndromes were documented for 15 (88%) of 17 patients that died, including 14 with rostral-caudal progression; signs could not be evaluated in one patient that died in status epilepticus; the other death was due to respiratory failure in a patient with ascending JEV myelitis (Solomon *et al.*, 1998a). Patients with witnessed seizures were more likely to have signs compatible with herniation syndromes [27 (72%) of 40, versus 16 (16%) of 104; OR 11.42, 95% CI 4.53–29.44,  $P < 0.0001$ ], and were more likely to have those of rostral-caudal progression [14 (38%) of 40 versus five (7%) of 104; OR 10.66, 95% CI 3.19–37.77,  $P < 0.0001$ ]. Rostral-caudal progression was more frequent in patients with several seizures than in those with a single seizure [15 (52%) of 29 versus none of 12;  $P = 0.001$ ].

Upper gastrointestinal bleeds occurred in two patients and one had a nose bleed. Twelve (13%) patients with a good outcome, and 25 (50%) with a poor outcome developed pneumonia (OR 6.83, 95% CI 2.8–16.95,  $P < 0.0001$ ). Eight patients developed acute psychotic states during convalescence and were treated with major tranquilizers. Forty-eight patients were treated with diazepam and 23 with phenobarbitone; 67 patients received mannitol and three (with suspected bacterial meningitis) received steroids. Broad-spectrum antibiotics were used in 63 patients. Autopsy was possible on one 18-year-old male who had clinical signs of rostral-caudal progression, and had been ventilated for 74 h before being declared brain dead. At autopsy his brain weighed 1500 g and was so grossly swollen that it was not possible to distinguish any further features.

In a multiple logistic regression model, the combination of coma, multiple seizures, brainstem signs compatible with herniation syndromes and illness for 7 days or more gave the best prediction of outcome (Table 6), with 84% sensitivity, 87% specificity.

The presence of these four characteristics had a positive predictive value of 77% for poor outcome and a negative predictive value of 91% (OR 35.88, 95% CI 12.46–108.15,

$P < 0.001$ ). Forward selection and backward elimination procedures generated the same model, indicating its robustness. The Hosmer–Lemeshow statistic indicated a non-significant lack of fit ( $\chi^2 = 6.408$ ,  $P = 0.379$ ).

## Discussion

Since the 1870s, when epidemics of encephalitis were first described in Japan, the importance of JE has grown considerably (Innis, 1995; Tsai and Halstead, 1998). The geographical area affected by the virus has expanded to include the Indian subcontinent, Southeast Asia, most of China, the Western Pacific and recently northern Australia (Solomon *et al.*, 2000a). Closely related flaviviruses with virological, epidemiological and clinical similarities, such as West Nile virus, are also becoming more important (Briese *et al.*, 1999; Solomon and Cardoso, 2000). There is no antiviral treatment against JE. The mortality is high (20–30% in most settings) and the majority of survivors have severe neurological sequelae, which include a polio-like flaccid paralysis (Misra and Kalita, 1997; Solomon *et al.*, 1998a). Although an expensive formalin-inactivated vaccine (Hoke *et al.*, 1988), and newer live attenuated vaccine (Hennessy *et al.*, 1996) are available in some areas, the majority of the 2.8 billion people living in affected regions are not vaccinated, and JE looks likely to remain an important public health problem into the 21st century.

We therefore conducted a clinicopathological study to identify factors associated with a poor outcome that might be reversible with treatment. Previously, a variety of parameters has been associated with a poor outcome in JE, including isolation of virus from the CSF, low levels of JE virus-specific IgM and IgG in CSF and serum, immune complexes in the CSF, short prodromal illness, depressed level of consciousness, abnormal breathing and decerebrate posturing (Burke *et al.*, 1985; Kumar *et al.*, 1990; Desai *et al.*, 1994). However, none of these is currently amenable to treatment. Our results suggest that seizures, hypoxic cerebral metabolism, raised ICP, and possibly brainstem herniation may all play a role in the pathophysiology of JE. Although various studies have implicated parts of this pathophysiological pathway in a range of CNS infections, this is the first time

they have been investigated in a large prospective series of patients infected with a single agent.

Seizures complicate several nervous system infections, including bacterial meningitis (Horwitz *et al.*, 1980; Pike *et al.*, 1990), herpes simplex encephalitis (Whitley *et al.*, 1986; Kennedy, 1988) and cerebral malaria (White *et al.*, 1988; Crawley *et al.*, 1996). A high incidence of seizures has been noted in children with JE before (Poneprasert, 1989; Kumar *et al.*, 1990), but an association with poor outcome was not made, possibly because the number of seizures was not taken into account. In our study, a single seizure before admission was common, occurring in 40% of patients, and did not augur a poor outcome; however, repeated seizures and status epilepticus were strongly associated with severe sequelae and death. In >30% of patients with seizures, the clinical manifestations were subtle and could easily have been missed without EEG recording. Subtle motor seizures occur most commonly after prolonged status epilepticus (Shorvon, 1994), but may occur sooner in patients with severe encephalopathies (Treiman, 1995).

Even brief seizures are followed by a rise in ICP, probably secondary to increased cerebral blood flow and therefore volume (Minns and Brown, 1978). Uncontrolled seizures are associated with a variety of biochemical and metabolic consequences, including hypoxaemia, hypoglycaemia, hyperlactataemia, low CSF glucose, high CSF lactate, metabolic acidosis and CO<sub>2</sub> retention (Simpson *et al.*, 1977; Shorvon, 1994). These combine to cause cerebral oedema and a further rise in ICP. In our study, patients with recent seizures had higher CSF lactate/glucose ratios, and higher CSF OPs. We found patients with OP  $\geq 25$  cm were more likely to die. Raised ICP causes a reduction in cerebral blood flow, which, by exacerbating hypoxic cerebral metabolism and cerebral oedema, leads to a further rise in ICP. This cycle eventually precipitates downward displacement of the brainstem through the tentorial hiatus and foramen magnum (Plum and Posner, 1982).

Clinical signs compatible with transtentorial herniation were common among our patients with a poor outcome, occurring in 15 of the 17 that died. The interpretation of such signs can be difficult, as there may be overlap between signs of direct brainstem involvement and those of herniation syndromes. However, the presence of rostro-caudal progression in 14 of our patients, and the association with a high OP suggest that brainstem compression due to transtentorial herniation could have been an important mechanism leading to death (Plum and Posner, 1982), especially since in some patients the changes were reversed (if only temporarily) by treatment for intracranial hypertension. Herniation syndromes have not previously been recognized as important in JE (Innis, 1995). Most autopsy series of JE do not comment specifically on whether there are gross signs of herniation or subtle signs such as secondary brainstem haemorrhages (Zimmerman, 1946; Haymaker and Sabin, 1947), though in one series of seven patients no gross signs of uncal or

cerebellar herniation were found (Johnson *et al.*, 1985). Clearly more evidence on this important question is needed.

Interpretation of previous pathophysiological studies of viral encephalitis has been hampered by small sample sizes, their retrospective nature or the fact that a variety of different aetiological agents was responsible (Goitein *et al.*, 1983; Barnett *et al.*, 1988; Kennedy, 1988; Tasker *et al.*, 1988). Herpes simplex encephalitis has been studied in multi-centre treatment trials, and although seizures and raised ICP occur (Whitley *et al.*, 1982; Whitley *et al.*, 1986), they have not been shown to have any prognostic significance. This may be because the number of seizures was not taken into account, only their presence or absence (Whitley *et al.*, 1986). The detailed repeated examination and electrophysiological confirmation of subtle seizures conducted during our study in a single centre may not have been possible in multi-centre treatment trials. However, some of the factors which do carry a poor prognosis in herpes simplex encephalitis (deep coma score, prolonged illness and older age) (Whitley *et al.*, 1986) are similar to those for JE (Solomon and Vaughn, 2002).

Raised ICP and herniation syndromes have also been reported in bacterial meningitis and paediatric cerebral malaria (Williams *et al.*, 1964; Horwitz *et al.*, 1980; Newton *et al.*, 1991), and there has been considerable debate about the safety of LP in patients with suspected CNS infections. Although delayed LP and blind antibiotic treatment has been proposed for such patients (Newton *et al.*, 1991; Mellor, 1992; Rennick *et al.*, 1993), others have argued there is no strong evidence that herniation is precipitated by LP (White, 1991; Jones and Webb, 1993; Obaro, 1993). In diseases with high early mortality, some deaths will inevitably occur soon after LP, but in our study the shortest interval between LP and death was 12 h. A policy of delayed LP and blind antibiotic treatment for all patients with suspected CNS infections would hamper diagnosis, might lead to problems with partial treatment of bacterial meningitis and the development of antibiotic resistance (Kwiatkowski *et al.*, 1991), and is unlikely to be practical in countries with scarce resources (Greenwood, 1991). Guides have been proposed as to which patients with suspected bacterial meningitis should receive LP (Mellor, 1992; Pollard *et al.*, 1999). In paediatric cerebral malaria, no consensus has been reached but LP is still performed routinely without evidence of harm. Although post-mortem examination of the brain suggests an increased cerebral volume in paediatric cerebral malaria, there is no convincing evidence of herniation in most cases. Pheno-barbitone prophylaxis is associated with a worse outcome in this condition [probably because of respiratory depression (Crawley *et al.*, 2000)], and measures to reduce ICP have so far not been shown to provide sustained benefit (Newton *et al.*, 1997).

Both bacterial meningitis and cerebral malaria are treatable if diagnosed early. In JE there is no antiviral treatment. Our data indicate that seizures are important, and although they could simply be a marker of severe disease, and were not always controlled with diazepam, a study of anticonvulsant

prophylaxis may be justified. Phenobarbitone was not independently associated with a worse outcome in our study. In the past corticosteroids have been used for the treatment of JE, despite worries they may interfere with antiviral defences. The practice has become less common since a placebo-controlled trial failed to show any benefit or detriment (Hoke *et al.*, 1992), but their role remains uncertain. In some of our patients mannitol appeared to cause a transient improvement, and measures to control intracranial hypertension merit further consideration.

In summary, seizures, raised ICP and brainstem signs are common in JE and are strongly associated with a poor outcome. Whether they are a cause or simply an association cannot be determined for certain, but whilst no antiviral treatment is available for JE, measures aimed at controlling these secondary complications of infection may improve the outcome.

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