MAJOR ARTICLE

The Epidemiology, Clinical Features, and Long-Term Prognosis of Japanese Encephalitis in Central Sarawak, Malaysia, 1997–2005

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Background. Japanese encephalitis is a major public health problem in Asia. However, there is little data on the long-term outcome of Japanese encephalitis survivors.

Methods. We prospectively evaluated children with serologically confirmed Japanese encephalitis over an 8.3-year period. The patients were assessed and their outcomes were graded with a functional outcome score at hospital discharge and at follow-up appointments. We examined how patient outcome at hospital discharge compared with that at long-term follow-up visits, when changes in outcome occurred, and the prognostic indicators of the eventual outcome.

Results. One hundred and eighteen patients were recruited into the study, and 10 (8%) died during the acute phase of illness. At hospital discharge, 44 (41%) of the 108 patients who survived had apparent full recovery; 3 (3%) had mild, 28 (26%) had moderate, and 33 (31%) had severe neurological sequelae. Eighty six of the 108 patients were followed up for a median duration of 52.9 months (range, 0.9–114.9 months). During follow-up, 31 patients experienced improvement, but 15 patients experienced deterioration in their outcome grade. In most cases, assessment during the first 3–6 months after hospital discharge was predictive of the long-term outcome. More than one-half of the patients continued to experience neuropsychological sequelae and behavioral disorders. A combination of poor perfusion, Glasgow coma score $\leqslant 8$, and $\geqslant 2$ witnessed seizures predicted a poor long-term outcome with 65% sensitivity and 92% specificity.

Conclusions. Neurological assessment of Japanese encephalitis survivors at hospital discharge does not predict long-term outcome. Seizures and shock are treatable risk factors for a poor outcome at hospital discharge and at long-term follow-up visits.

Japanese encephalitis (JE), a mosquito-borne viral infection of the CNS, is a major public health problem in Asia, where it accounts for up to 50,000 cases and 15,000 deaths annually [1, 2]. The causative agent, JE virus (JEV; genus *Flavivirus*, family *Flaviviridae*) is transmitted among birds, pigs, and other vertebrate hosts by *Culex* species mosquitoes that breed in rice fields and stagnant water. Humans, as incidental dead-end hosts, become infected when they encroach on the enzoonotic cycle. In parts of Asia where JE is endemic, it is principally a disease of children living in rural areas [1, 2]. The clinical syndromes caused by the virus include a mild nonspecific febrile illness, febrile seizures, aseptic meningitis, encephalitis, and a poliomyelitis-like illness. The acute case fatality rate is ~30%, and up to 50% of the survivors develop neurological sequelae [1–3]. Several studies have examined the neurological outcome of JE survivors soon after hospital discharge, but there are few data on long-term outcome. Therefore, we studied a cohort of patients with JE in Sarawak, Malaysia, paying particular attention to how their outcome at hospital discharge compared with that at long-term follow-up visits, when the changes in outcome occurred, and the prognostic indicators of the eventual outcome.

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Table 1. Comparison of clinical and demographic characteristics for 118 patients with Japanese encephalitis, by outcome group at hospital discharge and at long-term follow-up examination.

Characteristic	Outcome group at hospital discharge			Outcome group at long-term follow-up examination			
	Poor outcome (n = 41)	Better outcome (n = 77)	P	Poor outcome (n = 23)	Better outcome (n = 73)	Lost to follow-up (n = 22)	P
Male sex	25 (61)	44 (57)	.837	15 (65)	40 (55)	14 (64)	.523
Ethnic origin							
Chinese	2 (5)	10 (13)	.213	2 (9)	7 (10)	3 (14)	>.99
Iban	33 (80)	55 (71)	.393	16 (70)	57 (78)	15 (68)	.579
Malay/Melanau	3 (7)	9 (12)	.539	3 (13)	7 (10)	2 (9)	.699
Orang Ulu	1 (2)	2 (3)	>.99	0 (0)	1 (1)	1 (5)	>.99
Other	2 (5)	1 (1)	.277	2 (9)	1 (1)	1 (5)	.142
Age, mean years (range)	6.7 (1.8–11.5)	6.9 (0.3–2.0)		6.2 (1.8–11.5)	6.9 (0.3–12.0)	7.4 (0.5–12.0)	.310
Fever	41 (100)	75 (97)	.543	23 (100)	72 (99)	21 (95)	>.99
Duration of fever, mean days (range)	3.2 (1–7)	3.6 (1–14)		3.0 (1–7)	3.6 (1.0–14.0)	3.6 (1.0–12.0)	.158
History of viral prodrome	4 (10)	20 (26)	.065	2 (9)	19 (26)	3 (14)	.143
Headache	23 (56)	52 (68)	.304	10 (43)	50 (68)	15 (68)	.056
Neck pain	7 (17)	14 (18)	.918	2 (9)	17 (23)	2 (9)	.148
Photophobia	1 (2)	6 (8)	.419	0 (0)	4 (5)	3 (14)	.569
Abnormal behavior	13 (32)	21 (27)	.770	7 (30)	21 (29)	6 (27)	.913
Irritability	15 (37)	21 (27)	.403	9 (39)	19 (26)	8 (36)	.346
Alertness	5 (12)	19 (25)	.173	3 (13)	13 (18)	8 (36)	.754
Lethargy	32 (78)	50 (65)	.283	22 (96)	49 (67)	11 (50)	.014
Drowsiness	32 (78)	45 (58)	.054	19 (83)	48 (66)	10 (45)	.202
Confusion	16 (39)	26 (34)	.714	7 (30)	30 (41)	5 (23)	.503
Unconsciousness	9 (22)	5 (6)	.018	9 (39)	2 (3)	3 (14)	<.001
History of seizure	33 (80)	38 (49)	.002	18 (78)	37 (51)	16 (73)	.037
History of >3 seizures	9 (22)	5 (6)	.018	6 (26)	4 (5)	4 (18)	.011
History of prolonged convulsion	9 (22)	6 (8)	.056	8 (35)	2 (3)	5 (23)	<.001
Limb weakness							
Any	9 (22)	18 (23)	.957	6 (26)	18 (25)	3 (14)	.891
Focal	6 (15)	5 (6)		3 (13)	7 (10)	1 (5)	
Generalized	3 (7)	13 (17)		3 (13)	11 (15)	2 (9)	
Poor feeding	35 (85)	60 (78)	.468	21 (91)	57 (78)	17 (77)	.224
Diarrhea	2 (5)	2 (3)	.609	1 (4)	1 (1)	2 (9)	.424
Vomiting	22 (54)	47 (61)	.563	13 (57)	45 (62)	11 (50)	.847
Poor urine output	15 (37)	20 (26)	.322	12 (52)	20 (27)	3 (14)	.052
Living in rural area	39 (95)	59 (77)	.022	18 (78)	58 (79)	17 (77)	>.99
Living near pigs and/or chickens	14 (34)	27 (35)	.918	12 (52)	23 (32)	6 (27)	.122

NOTE. Data are no. (%) of patients, unless otherwise indicated.

PATIENTS AND METHODS

Setting. Our study was conducted at Sibu Hospital (Sarawak, Malaysia), which serves Sibu town and receives referrals from smaller district hospitals in Central Sarawak (total population, 650,000; population aged ⩽12 years, 180,000) [4]. The study was approved by the Director of Health for Sarawak and the Ethics Committee of the Liverpool School of Tropical Medicine (Liverpool, UK). Informed consent was obtained from each child's parent or guardian.

Study period and definition. From November 1999 through May 2005, children with JE were observed as part of a study involving all children with suspected CNS infections. CNS infections were suspected if patients had a fever or history of fever and at least 1 of the following signs and symptoms: reduced level of consciousness (e.g., lethargy, drowsiness, or coma); severe headache; neck stiffness; limb paralysis; tense anterior fontanelle; and seizures [5, 6] (except for simple febrile seizures) [7]. Following CSF examination, children with CSF pleocytosis (WBC count, >5 cells/μL) and microscopy and culture findings negative for bacteria were considered to have suspected viral CNS infection. They were classified as having aseptic meningitis if they were fully conscious with no focal

Table 2. Comparison of findings at initial examination and laboratory results for 118 patients with Japanese encephalitis, by outcome group at hospital discharge and at long-term follow-up examination.

Variable	Outcome group at hospital discharge			Outcome group at long-term follow-up examination			
	Poor outcome (*n* = 41)	Better outcome (*n* = 77)	*P*	Poor outcome (*n* = 23)	Better outcome (*n* = 73)	Lost to follow-up (*n* = 22)	*P*
Examination finding							
Ill appearance	38 (93)	57 (74)	.028	22 (96)	58 (79)	15 (68)	.107
Dehydration	21 (51)	31 (40)	.344	14 (61)	29 (40)	9 (41)	.124
Intubation at referring hospital	6 (15)	0 (0)	.001	5 (22)	1 (1)	0 (0)	.003
Respiratory abnormality	5 (12)	4 (5)	.273	3 (13)	4 (5)	2 (9)	.353
Respiratory rate, mean breaths per min (range)	32 (20–52)	31 (18–48)	.373	33.9 (20–52)	30.5 (18–48)	30.5 (20–44)	.052
Poor perfusion	20 (49)	22 (29)	.048	15 (65)	22 (30)	5 (23)	.006
Heart rate, mean beats per min (range)	121 (72–168)	110 (76–170)	.005	124.4 (92–170)	110.4 (72–146)	108.3 (76–146)	.003
Neck stiffness	29 (71)	48 (62)	.478	15 (65)	51 (70)	11 (50)	.872
Kernig's sign	4 (10)	9 (12)	>.99	2 (9)	9 (12)	2 (9)	>.99
Altered sensorium	38 (93)	51 (66)	.003	22 (96)	52 (71)	15 (68)	.032
Modified Glasgow coma score, median value (range)	9 (3–15)	13 (3–15)	<.001	6 (3–15)	12 (6–15)	12.5 (7–15)	<.001
Modified Glasgow coma score ⩽8	17 (41)	12 (16)	.004	14 (61)	11 (15)	4 (18)	<.001
Seizures witnessed at admission	19 (46)	8 (10)	<.001	16 (70)	9 (12)	2 (9)	<.001
Abnormal muscle tone							
Overall	31 (76)	30 (39)	<.001	22 (96)	31 (42)	8 (36)	<.001
Hypertonia	23 (56)	20 (26)		15 (65)	20 (27)	8 (36)	
Hypotonia	8 (20)	10 (13)		7 (30)	11 (15)	0 (0)	

Abnormal limb reflexes							
Overall	33 (80)	32 (42)	<.001	22 (96)	32 (44)	11 (50)	<.001
Hyperreflexia	25 (61)	28 (36)		16 (70)	20 (27)	7 (32)	
Hypoflexia or areflexia	8 (20)	14 (18)		6 (26)	12 (16)	4 (18)	
Abnormal posture							
Overall	11 (27)	7 (9)	.022	9 (39)	5 (7)	4 (18)	<.001
Decortication	8 (20)	4 (5)		3 (13)	1 (1)	1 (5)	
Decerebration	3 (7)	2 (3)		6 (26)	3 (4)	3 (14)	
Opisthotonus	0 (0)	1 (1)		0 (0)	1 (1)	0 (0)	
Limb weakness							
Overall	23 (56)	11 (14)	.894	16 (70)	13 (18)	5 (23)	<.001
Focal	5 (12)	4 (5)		4 (17)	5 (7)	0 (0)	
Generalized	18 (44)	7 (9)		12 (52)	8 (11)	5 (23)	
Clonus	2 (5)	1 (1)	>.99	2 (9)	0 (0)	1 (5)	.056
Presence of pyramidal signs	33 (80)	36 (47)	<.001	22 (96)	36 (49)	11 (50)	<.001
Hepatomegaly	5 (12)	8 (10)	.765	3 (13)	9 (12)	1 (5)	>.99
Laboratory findings							
Hemoglobin level, mean g/dL (range)	11.2 (8.1–13.9)	11.4 (7.9–15.4)	.545	10.9 (8.1–13.9)	11.2 (7.9–13.9)	11.7 (9.5–15.4)	.309
WBC count, mean cells/μL (range)	14362 (3900–38,900)	16,241 (2300–36,900)	.196	15,520 (7000–25,900)	16,650 (2300–38,900)	14,109 (3900–30,400)	.561
Platelet count, mean platelets/μL	279950 (113,000–465,000)	295,361 (420,000–863,000)	.453	290,000 (148000–465000)	297,652 (42000–86,3000)	292,818 (108000–544000)	.781
Sodium level at hospital admission, mean mmol/L (range)	134 (124–144)	135 (124–163)	.308	134 (124–140)	135 (124–163)	135 (126–145)	.223
Nadir sodium level during hospitalization, mean mmol/L (range)	130 (117–144)	133 (109–163)	.004	129 (117–137)	133 (109–163)	133 (125–142)	.009
CSF cell count, median cells/μL (range)	182 (2–1333)	189 (0–1515)	.905	22 (3–1333)	80 (0–1515)	38 (1–710)	.185
CSF protein level, mean g/dL (range)	0.92 (0.12–3.95)	0.73 (0.1–6.1)	.201	0.73 (0.12–2.55)	0.81 (0.1–6.1)	0.78 (0.12–3.95)	.645
CSF/serum glucose ratio, mean value (range)	0.66 (0.27–1.09)	0.62 (0.12–1.08)	.360	0.65 (0.31–1.09)	0.65 (0.2–1.04)	0.64 (0.31–1.08)	.950

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Table 3. Progression and management for 118 patients with Japanese encephalitis, by outcome group at hospital discharge and at long-term follow-up examination.

Variable	Outcome group at hospital discharge			Outcome group at long-term follow-up examination			
	Poor outcome (n = 41)	Better outcome (n = 77)	P	Poor outcome (n = 23)	Better outcome (n = 73)	Lost to follow-up (n = 22)	P
Progress							
Had convulsion anytime after hospital admission	29 (71)	19 (25)	<.001	19 (83)	22 (30)	7 (32)	<.001
Developed status epilepticus anytime after hospital admission	17 (41)	7 (9)	<.001	13 (57)	7 (10)	4 (18)	<.001
Management							
Mechanical ventilation							
Overall	24 (59)	7 (9)	<.001	20 (87)	7 (10)	4 (18)	<.001
Elevated intracranial pressure	6 (15)	0 (0)		5 (22)	1 (1)	0 (0)	
Respiratory failure	3 (7)	2 (3)		3 (13)	1 (1)	1 (5)	
Status epilepticus	15 (37)	5 (6)		12 (52)	5 (7)	3 (14)	
Inotropic support	24 (59)	18 (23)	<.001	20 (87)	16 (22)	6 (27)	<.001
Mannitol infusion	23 (56)	11 (14)	<.001	17 (74)	14 (19)	3 (14)	<.001
Anticonvulsant	39 (95)	59 (77)	<.022	22 (96)	58 (79)	18 (82)	.107

NOTE. Data are no. (%) of patients.

neurological signs. Children with CSF pleocytosis, Glasgow coma score ⩽13, focal neurological signs, or prolonged seizures were classified as having viral encephalitis; if they had these clinical features but no CSF pleocytosis, they were classified as having febrile encephalopathy.

Data collection. Details of the patients' history and clinical examination findings were recorded on standardized forms. Because we were concerned that dehydration and poor perfusion might contribute to a poor outcome in JE, we carefully documented the patients' peripheral perfusion status. Poor perfusion was defined by the presence of a prolonged capillary refill time (>2 sec), weak peripheral pulses, or cold limbs. Blood samples were obtained for routine investigations and flavivirus serological testing. CSF samples were examined for cell count and differential cell count, protein level, and glucose level and underwent Gram staining, bacterial culture, and viral studies. If there was a strong clinical suspicion of viral CNS infection but the initial CSF sample was acellular, a second lumbar puncture was performed. Lumbar punctures were delayed for those patients who were severely unwell.

Serological diagnosis. Because dengue virus that has serological cross reactivity with JEV is endemic in Sarawak, we tested CSF and serum samples using an IgM-capture ELISA that distinguishes between responses to these 2 viruses [8]. Paired serum samples (obtained at hospital admission and at day 7, at discharge from the hospital, or after death) and either 1 CSF specimen or paired CSF specimens were tested for IgM against dengue virus and JEV in parallel. A sample was considered to be IgM positive for JEV if the optical density against JEV was higher than that against dengue virus [8]. Seroconversion from a negative acute-phase sample to a positive second sample or an increasing IgM optical density was considered to be evidence of acute JEV infection; if such changes occurred in serum samples only, with negative results for paired CSF samples, they were considered to be diagnostic of an acute peripheral JEV infection and were not included in this study. JEV-specific IgM in CSF samples was diagnostic of JEV CNS infection even if the acute-phase serum sample had negative results. A decreasing IgM optical density in serum samples was considered to be evidence of recent infection. A low IgM optical density in serum samples obtained from children who had been recently vaccinated against JEV with the formalin-inactivated mouse brain vaccine was occasionally noted and was ascribed to vaccination.

Management. The patients were managed according to the hospital management protocol. This included use of empirical intravenous antibiotics in patients with possible bacterial infection and intravenous phenytoin or phenobarbitone in patients who had a history of seizures or in patients with fever and reduced consciousness. Patients with witnessed seizures were treated promptly with intravenous midazolam. Patients with status epilepticus were treated with intravenous midazolam infusion and/or intravenous thiopentone infusion and received mechanical ventilation. Where necessary, intravenous inotropic support and volume expanders were used to ensure adequate tissue perfusion. Intravenous mannitol infusion and/or mechanical ventilation were used for patients with signs of elevated intracranial pressure.

Outcome assessment. All patients with confirmed JE were followed up prospectively and were assessed by a member of the study team. The parents were interviewed and the patients were assessed using a standardized assessment protocol (mod-

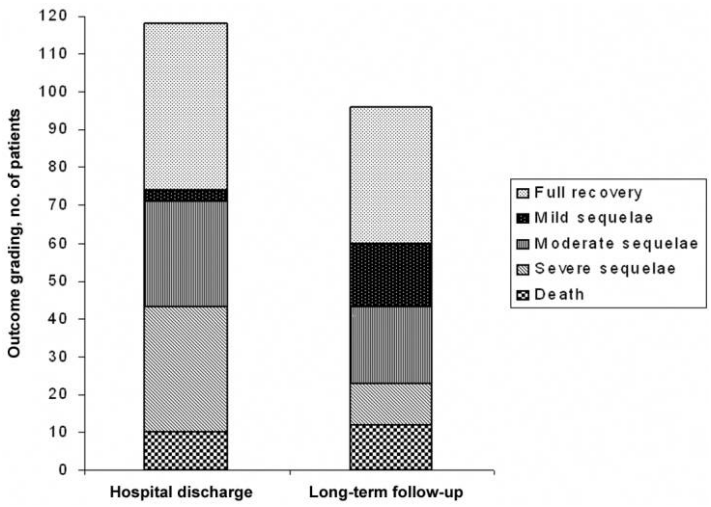

Figure 1. The outcome grading of 118 children with Japanese encephalitis at hospital discharge and at long-term follow-up evaluation. A total of 22 patients were lost to follow-up.

ified from one developed earlier) before hospital discharge, 3–6 months after hospital discharge, and every 3–12 months thereafter, depending on the patients' conditions and their accessibility to the hospital. The outcome of JEV infection was graded with a functional outcome score, as follows: I, death; II, severe sequelae greatly impairing function and incompatible with independent living; III, moderate sequelae mildly affecting function (including seizures) but compatible with independent living; IV, minor sequelae including altered personality or clinical signs not affecting functions; and V, full recovery and normal neurological examination findings [5].

In addition to the prospective study of patients with acute JE, which began in November 1999, we also studied, at follow-up, patients with JE who had been admitted to our hospital previously (from February 1997, when diagnostic testing was first instituted, through October 1999). Patients who had been lost to follow-up were contacted again. Medical records were reviewed and clinical data were extracted using a standardized format. The clinical and laboratory diagnostic methods for patients admitted to the hospital from February 1997 through October 1999 were similar to those for patients admitted to the hospital in November 1999 and after. In October 2006, we again contacted all patients who had missed follow-up appointments for a final assessment.

Statistical analysis. For the purpose of the analysis, the grading of the final outcome was defined as that at the most recent follow-up assessment. Patients with grade I (death) or grade II (severe sequelae) were considered to have a poor outcome, whereas patients with grades III, IV, and V (moderate, mild, or no sequelae) were considered to have a better outcome [5, 9]. Normally distributed data were compared using Student's *t* test; data that were not normally distributed were compared by the Mann-Whitney *U* test (Staview 4.02; Abacus Concepts). Differences between proportions were tested using the χ^2 test with Yates' correction or Fisher's exact test (Epi-Info 2002; Centers for Disease Control and Prevention). Because we were performing multiple comparisons to look for possible parameters associated with a poor outcome, we considered $P < .05$ to indicate a trend and $P < .01$ to be statistically significant in univariate analysis. Variables that were associated with a poor outcome in univariate analyses were examined in a stepwise logistic regression (SPSS, version 13; SPSS).

RESULTS

Epidemiology. Approximately 900 patients with suspected CNS infection were admitted to the hospital over an 8.3-year period. Of these patients, 118 (69 [58%] of whom were male) had confirmed JEV neurological infection with JEV IgM found in CSF samples; 102 of 111 patients had JEV IgM found in serum samples. The annual incidence of JE in central Sarawak was estimated to be 7.9 cases per 100,000 children aged ≤12 years. Of the 118 patients, 75 (64%) were observed prospectively from their initial hospital admission (1999–2005 cohort); for 43 patients, clinical features present at the initial hospital admission were assessed retrospectively from hospital notes (1997–1999 cohort). There was no significant difference between the 2 cohorts with respect to clinical features at hospital admission or discharge or with respect to length of follow-up (data not shown). All patients participated in the study.

The majority (73) of the patients were 5–10 years of age (tables 1–3). Two patients were <12 months of age; both of these patients presented with febrile seizures (at 3.4 months and 6 months of age). Acute encephalitis was the most common

Table 4. Outcome at hospital discharge for 118 patients with Japanese encephalitis.

Outcome grade	No. (%) of patients
Death	10 (8)
Severe sequelae[a]	
Overall	33 (28)
Severe cognitive impairment with spastic quadriparesis	14
Severe cognitive impairment with no gross motor impairment	2
Mutism with quadriparesis[b]	9
Mutism	4
Mutism and hemiplegia	1
Mentally normal but bed-bound because of quadriparesis	2
Isolated swallowing difficulty requiring nasogastric tube feeding	1
Moderate sequelae	
Overall	28 (24)
Paraplegia/diplegia (spastic)	1
Quadriparesis with mild cognitive impairment	1
Quadriparesis, walks with help	2
Quadriparesis, walks alone	1
Hemiparesis, walks with help	1
Hemiparesis, walks alone	1
Monoplegia (splastic, upper limb)	1
Reduced speech, walks with help	2
Reduced speech, walks alone	4
Reduced speech, labile emotion	1
Reduced speech and ataxic gait	2
Ataxia	4
Generalized weakness and requiring help to walk	6
Seventh nerve upper neuron palsy	1
Mild sequelae	
Overall	3 (3)
Blunted affect	1
Upper neuron signs (hyperreflexia)	1
Parkinsonian features (cogwheel rigidity)	1
Full recovery	44 (37)

[a] A total of 20 of 33 patients with severe sequelae required nasogastric tube feeding.
[b] One patient had parkinsonian sequelae, characterized by cogwheel rigidity, mask-like facies, and hand tremor.

presentation (97 patients; 82%), followed by febrile encephalopathy (10 patients; 8%), aseptic meningitis (8 patients; 7%), and febrile seizures (3 patients; 3%). The acute case–fatality rate was 8% (10 of 118 patients). Long-term outcome data were available for 96 (81%) of the 118 patients (59 of whom were from the 1999–2005 cohort); this included 10 patients who died. The median number of follow-up visits per patient throughout the study was 2 (range, 1–6 visits). The median duration of follow-up was 52.9 months (range, 0.9–114.9 months). The final outcome of the remaining 22 patients (16 of whom were from the 1999–2005 cohort) was uncertain, because they were lost to follow-up. However, those patients who were lost to follow-up were similar to those patients who were followed-up; 61 (64%) of 96 patients who were followed up had a good outcome at hospital discharge, compared with 16 (73%) of 22 patients who were not followed up ($P = .57$).

Comparison of outcome at hospital discharge and long-term follow-up. Figure 1 shows the distribution of the outcome grading of all patients at hospital discharge and at long-term follow-up visits. At hospital discharge, 44 (37%) of the 118 patients had apparently made a full recovery, and 3 (3%) had mild, 28 (24%) had moderate, and 33 (28%) had severe neurological sequelae (table 4). Of the 86 patients who had follow-up assessment, 36 (42%) had full recovery, and 48 (56%) had neurological sequelae (17 [20%] had mild, 20 [23%] had moderate, and 11 [13%] had severe neurological sequelae at their last assessment) (table 5).

Figure 2 shows the changes in outcome grading at follow-

Table 5. Long-term outcome for 86 patients with Japanese encephalitis.

Outcome grade	No. (%) of patients
Death	2 (2)
Severe sequelae	
Overall	11 (13)
Severe cognitive impairment with spastic quadriparesis	9
Severe cognitive impairment, microcephaly, and marked hyperactivity	1
Mentally normal but bed-bound because of severe diplegia	1
Moderate sequelae	
Overall	20 (23)
Mild cognitive impairment with altered personality	4
Mild cognitive impairment with hand tremor	2
Mild cognitive impairment, altered personality with psychobehavioral problem	2
Mild cognitive impairment, dysarthria, and right hand tremor	1
Mild cognitive impairment, altered personality, and hemiparesis	1
Altered personality with lower limb wasting	1
Emiparesis, isolated	3
Emiparesis, with dystonia	1
Monoplegia, upper limb	1
Monoplegia, lower limb	1
Monoplegia, upper limb and dystonia	1
Facial twitch and dysphonia	1
Seizure, frontal release signs, and brisk reflexes	1
Mild sequelae	
Overall	17 (20)
Upper motor neuron signs[a]	5
Mild cerebellar signs[b]	2
Frontal release signs	1
Upper motor neuron signs and cerebellar signs[a]	1
Upper motor neuron signs, cerebellar signs, and frontal release signs[a]	1
Altered personality	4
Blunted affect	1
Hand tremor	1
Mild hyperactivity	1
Full recovery	36 (42)

[a] Upper motor neuron signs include extensor plantar, clonus, and hyperreflexia.
[b] Mild cerebellar signs include nystagmus, intentional tremor, and dysdiadochokinesis.

up for different patient groups. A total of 27 (31%) of the 86 patients who returned for follow-up examination had severe sequelae at hospital discharge; of these 27 patients, 6 (22%) had full recovery, 1 (4%) had mild sequelae, 8 (30%) had moderate sequelae, 10 (37%) had severe sequelae, and 2 (7%) died 12 and 72 months after discharge. A 3-year-old boy who had presented with encephalitis and status epilepticus appeared to have made a full recovery before hospital discharge; however, 73 months later, he had microcephaly and hyperactive behavior that required constant adult supervision, and therefore, he was classified as having severe sequelae. Four patients had moderate sequelae on follow-up examination; of these, 2 (who had presented with encephalitis) had mild cognitive impairment and altered personality, 1 (who had presented with febrile seizures) had isolated mild cognitive impairment, and 1 (who had presented with encephalitis) had epilepsy, brisk reflexes, and frontal release signs. Eight patients (4 of whom had initially presented with encephalitis, 3 with aseptic meningitis, and 1 with febrile encephalopathy) had mild sequelae on follow-up with subtle neurological deficits such as upper neuron signs, frontal release signs, or hand tremor. The 8 patients with moderate sequelae at hospital discharge (6 of whom had presented with encephalitis and 2 of whom had presented with febrile encephalopathy) recovered fully. Three had been ataxic at hospital discharge, 2 had been quiet and withdrawn, and 3 had required assistance for walking because of lower limb weakness, quadriparesis, or generalized body weakness (1 patient each). The 6 patients with full recovery from severe sequelae at hospital

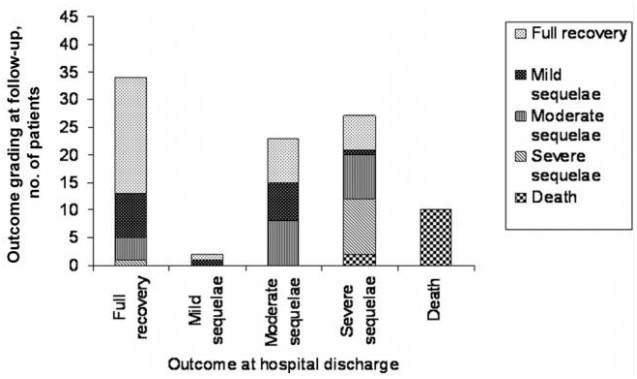

Figure 2. A comparison of patient outcome grading at hospital discharge with outcome at long-term follow-up evaluations for 86 children with Japanese encephalitis.

discharge included 5 who had been bed-bound with quadriparesis and 1 patient with impaired cognitive function who required nasogastric feeding. Among these patients, 4 were also aphasic, and 1 had Parkinsonian sequelae.

Fifteen (65%) of 23 patients with moderate sequelae at hospital discharge who were followed up had improved significantly; 8 had full recovery, and 7 had mild sequelae. In contrast, 13 (38%) of 34 patients who had apparent full recovery at hospital discharge were found to have varying degrees of neurological sequelae at long-term follow-up visits.

Although most patients improved after hospital discharge, the degree of improvement was not necessarily sufficient to effect a revision in the outcome grading. For example, 10 (30%) of 33 patients with severe sequelae at hospital discharge had better cognitive function, improved limb function, or the ability to feed normally by the time of follow-up, but their grading remained unchanged, because they remained dependent as the result of a severe spastic quadriplegia.

Of 37 patients who later had mild and moderate sequelae, 14 (38%) had altered personality after JE. Their parents reported poor temperament, impulsiveness, aggressive behavior, loss of enthusiasm and motivation, and becoming quieter and less communicative. In addition, 11 (30%) of the parents reported that their children experienced impaired memory, particularly short-term memory.

Of the 86 patients who had follow-up examination, 48 patients (56%) were school children when infected with JEV. Six (13%) of these 48 children had never returned to school because of severe physical disabilities; 16 (38%) of the remaining 42 had marked deterioration in school performance, resulting in 6 of them having to stop schooling; and only 20 (48%) of the 42 children performed satisfactorily. Details about schooling were available for 30 of the 38 patients who had JE at a preschool age (i.e., <7 years of age). Five children had never attended school because of severe disability; 5 did poorly in school, resulting in 2 of them having to stop schooling. The remaining 20 children performed satisfactory. Epilepsy was found in 7 (8%) of 86 patients at follow-up examinations.

Comparison of outcome grading at early follow-up and late follow-up examinations. Of the 86 patients who had follow-up, 24 (28%) had both an early follow-up assessment (within the first 3–6 months after hospital discharge) and a late follow-up assessment (>6 months after hospital discharge). Eighteen (75%) of these 24 patients had identical grading in their early and late follow-up assessments. For the remaining 6 patients (25%), there was a change in the grading for the late follow-up assessments (improvement in 4 patients and deterioration in 2 patients).

Predictors of poor outcome at hospital discharge and at long-term follow-up examinations. In tables 1–3, the clinical features of the patients who were classified as having poor outcome at hospital discharge are compared with the clinical

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

Variable	Acute phase, adjusted OR (95% CI)	*P*	Long-term follow-up examination, adjusted OR (95% CI)	*P*
Poor perfusion	…		8.53 (1.88– 38.79)	.006
Glasgow coma score ⩽8	…		5.17 (1.10–24.24)	.037
⩾2 Witnessed convulsions	7.6 (3.1–18.5)	<.001	15.64 (3.50–69.81)	<.001
Nadir sodium level ⩽135 mmol/L	4.0 (1.3–12.3)	.016	…	

NOTE. Parameters entered into the model included history of unconsciousness, poor perfusion, Glasgow coma score ⩽8 and presence of pyramidal signs on initial examination, ⩾2 witnessed seizures, and nadir serum sodium level ⩽135 mmol/L. Terms were entered into the model only if they were statistically associated with poor outcome ($P < .05$). Both forward selection and backward elimination methods were used. Forward selection and backward elimination procedures generated the same model, indicating its robustness. The Hosmer-Lemeshow statistics indicated a nonsignificance of lack of fit ($\chi^2 = 2.840$; $P = .725$). Repeating the analysis by including the duration of follow-up in the model did not alter the independent risk factors associated with poor final outcome. A similar approach was taken to look for parameters predictive of poor outcome at hospital discharge and found that ⩾2 witnessed seizures and nadir serum sodium level ⩽135 mmol/L were independent factors found to be predictive of a poor outcome at hospital discharge.

features of patients with better outcome. Patients with a poor outcome at hospital discharge were more likely than others to have seizures before hospital admission, to have seizures witnessed at admission, to have a faster heart rate, to have required intubation at referring hospitals, to have reduced Glasgow coma score, to have lower median Glasgow coma score, and to have abnormal motor signs (abnormal muscle tone, abnormal limb reflexes, and limb weakness).

Tables 1–3 also show how the presenting features and progress were related to the patients' outcome at the final follow-up examination. Many of the indicators for a poor prognosis at hospital discharge were also indicators for a poor outcome at long-term follow-up examination. These included deep coma score, witnessed seizures at admission, continued seizures after hospitalization, status epilepticus, abnormal muscle tone and reflexes, hyponatremia, and the need for mechanical ventilation and inotropic drugs. Abnormal body posture and limb weakness at presentation that were not associated with poor outcome at hospital discharge became important indicators for poor long-term outcome. There was no difference in the median length of follow-up between patients with a poor outcome and those with a better outcome at long-term follow-up examination (median duration, 51.7 months [range, 6.1–84.3 months] vs. 54.0 months [range, 0.9–114.9 months]; $P = .682$).

To find the best prediction of poor outcome at long-term follow-up examination, parameters significant in univariate analysis were entered into a multiple logistic regression model. A combination of poor perfusion, Glasgow coma score $\leqslant 8$, and $\geqslant 2$ episodes of witnessed seizures gave the best prediction of poor outcome, with 65% sensitivity and 92% specificity (table 6). The presence of these 3 characteristics had a positive predictive value of 71% and a negative predictive value of 89% for poor outcome.

DISCUSSION

Most studies of JE report the survivors' outcome for periods of 6 weeks to 6 months after hospital discharge [9–15]. To our knowledge, only 3 studies have followed up survivors for >1 year, including a study involving 39 patients who were followed up for up to 421 days [16], a study in which 55 patients were followed up for up to 2 years [17], and a study in which 78 patients were followed up for 6–27 years [18]. The paucity of long-term outcome data is partly related to the difficulty of following up JE survivors, because most patients live in rural areas with limited access to health care facilities [16]. Most studies that examined prognostic indices related them to outcome at hospital discharge, rather than to long-term outcome, although the latter is more important.

Our study provides further insight into the long-term prognosis of JE survivors. Most patients experienced improvement after hospital discharge; some experienced remarkable recovery, and others did not recover sufficiently to become independent. More than one-half of the survivors continue to experience a spectrum of neuropsychological and behavioral disorders. Our findings are similar to those of Baruah et al. [16], who reported improvement among survivors up to 330 days after hospital discharge; however, many of our cohort who were apparently healthy at hospital discharge later experienced other difficulties (in particular, impairment of memory and changes in behavior and personality). Similar late changes were also seen in patients infected with West Nile virus, a closely related flavivirus [19, 20]. Marked deterioration in school performance and loss of enthusiasm and motivation were also common among JE survivors. Our results show that neurological assessment of JE survivors at hospital discharge does not entirely predict their long-term outcome, but assessment at 3–6 months after hospital discharge is predictive of long-term outcome in three-quarters of patients. Neurological deterioration can occur several years after the initial infection, so survivors should have regular long-term follow-up evaluations to identify and manage any disability in a timely fashion.

A range of clinical features has been associated with a poor outcome of JE at hospital discharge, including seizures, elevated intracranial pressure, deep coma, abnormal muscle tone and posture, and hyponatremia [5, 10, 21, 22]. Our study has confirmed most of these and has shown that seizures and reduced consciousness are also good predictors of long-term outcome. We also showed that features of shock (tachycardia and poor perfusion) were associated with poor outcome, which has not, to our knowledge, been reported previously in JE. Adequate cerebral perfusion pressure is vital in preventing secondary cerebral ischemia after a primary brain injury, and it is of greater importance than elevated intracranial pressure in determining the eventual outcome of children with nontraumatic coma [23]. Shock may develop because of marked dehydration before a child is hospitalized; but it can be compounded by some clinicians' fear that administering intravenous rehydration may exacerbate elevated intracranial pressure. Fluid management in patients with shock and acute brain injury is difficult, but our data and clinical experience suggest that adequate rehydration is vital.

Most of our patients were Ibans, who cultivate rice and commonly keep pigs close to their rural long houses. However, >15% of our patients originated from urban areas, possibly because, in Sarawak, rice fields and pigs are commonly found at the edges of towns. Although most patients in this study presented with encephalitis or febrile encephalopathy (as has been reported by many others previously), 8 (7%) of our patients had aseptic meningitis, and 3 (3%) had febrile seizures. Interestingly, we did not have patients who presented with a purely paralytic syndrome, although some encephalopathic pa-

tients had paralysis. Our mortality rate was low (8%, compared with the usual mortality rate of 20%–30%), possibly because of our modern intensive care unit.

In conclusion, we have shown that, although the clinical condition of many JE survivors' improves after hospital discharge, less than one-half make a full recovery, and approximately one-fifth experienced subsequent deterioration. Most changes in outcome occur within the first 3–6 months after hospital discharge, but some changes occur even after 2 years. We have confirmed the importance of seizures as a sign of poor prognosis, both for outcome at hospital discharge and long-term outcome. Our data suggest that clinical signs of shock are also associated with a poor outcome. Both of these factors are potentially amenable to treatment.

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