

Nipah encephalitis outbreak in Malaysia, clinical features in patients from Seremban

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ABSTRACT: Background: An outbreak of viral encephalitis occurred among pig industry workers in Malaysia in September 1998 to April 1999. The encephalitis was attributed to a new paramyxovirus, Nipah virus. This is a description of the clinical features of 103 patients treated in the Seremban Hospital with characterization of the prognostic factors. **Methods:** Clinical case records and laboratory investigations were reviewed. The case definition was: patients from the outbreak area, direct contact or in close proximity with pigs, clinical or CSF features of encephalitis. **Results:** The mean age was 38 years, 89% were male, 58% were ethnic Chinese, 78% were pig farm owners or hired workers. The mean incubation period was 10 days. The patients typically presented with nonspecific systemic symptoms of fever, headache, myalgia and sore throat. Seizures and focal neurological signs were seen in 16% and 5% respectively. In the more severe cases, this was followed by drowsiness and deteriorating consciousness requiring ventilation in 61%. Autonomic disturbances and myoclonic jerks were common features. The mortality was high at 41%. Systolic hypertension, tachycardia and high fever were associated with poor outcome. On the other hand, 40% recovered fully. As for the other 19%, the residual neurological signs were mostly mild. **Conclusion:** Nipah virus caused an encephalitis illness with short incubation period and high mortality. The prognosis for the survivors was good.

RÉSUMÉ: Encéphalite de Nipah en Malaisie: caractéristiques cliniques chez les patients de Seremban. Introduction: Il y a eu une écloison d'encéphalite virale chez les travailleurs de l'industrie du porc en Malaisie de septembre 1998 à avril 1999. L'encéphalite a été attribuée à un nouveau paramyxovirus, le virus de Nipah. Cet article décrit les caractéristiques cliniques et les facteurs pronostiques de 103 patients traités à l'Hôpital de Seremban. **Méthodes:** Les dossiers cliniques et les rapports de laboratoire ont été révisés. Les cas étaient définis comme suit: un patient provenant de la région touchée, un contact direct ou un voisinage immédiat avec des porcs, des caractéristiques d'encéphalite selon la clinique ou l'analyse du LCR. **Résultats:** L'âge moyen était de 38 ans, 89% étaient des hommes, 58% étaient d'ethnie chinoise, 78% étaient des propriétaires ou des travailleurs de l'industrie porcine. La période d'incubation moyenne était de 10 jours. Le patient type consultait pour des symptômes systémiques non spécifiques tels de l'hyperthermie, de la céphalée, des myalgies et un mal de gorge. Des convulsions et des signes neurologiques focaux ont été observés chez 16% et 5% respectivement. Dans les cas plus sévères, ces symptômes étaient suivis de somnolence et d'une détérioration de l'état de conscience nécessitant une ventilation assistée chez 61%. Des troubles neurovégétatifs et des secousses myocloniques étaient fréquemment observés. La mortalité était élevée, soit 41%. Une hypertension systolique, de la tachycardie et une forte fièvre étaient associées à un mauvais pronostic. D'autre part, 40% ont récupéré complètement. Chez 19%, les signes neurologiques résiduels étaient plutôt légers. **Conclusion:** Le virus de Nipah a causé une encéphalite dont la période d'incubation était courte et la mortalité élevée. Le pronostic chez les survivants était bon.

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From December 1998 to May 1999 there was an outbreak of encephalitis among the workers in the pig farm villages in Sikamat, Bukit Pelanduk (including Sungei Nipah and Kampong Jawa), Tanah Merah, Negri Sembilan State, as well as Sepang and Sungei Buloh, Selangor State in Central Peninsular Malaysia involving more than 200 patients. The outbreak was thought to have started in pig farming villages in Ulu Piah, Tambun and Ampang around Ipoh, about 200 km north of Kuala Lumpur, in September 1998.^{1,2} The outbreak also spread to involve abattoir workers in Singapore.^{3,4} Chua et al in an earlier report of three fatal cases with post-mortem findings has shown that the

encephalitis was due to a new strain of paramyxovirus closely related to Hendra virus, later named Nipah virus.^{5,6} During the epidemic, the patients were seen in two main Medical Centres, the University Malaya Medical Centre and Seremban Hospital.⁷⁻¹⁵

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Over the five months period from 26th December 1998 to 21st April 1999, 107 patients with encephalitis were admitted to Seremban Hospital. Four patients were transferred to another hospital during the acute illness for further care. This is the report of the 103 patients with Nipah encephalitis treated in this Medical Centre.

METHODS

Patients were defined as having Nipah encephalitis if they came from the outbreak areas, had direct contact or in close proximity with pigs, and who had features of encephalitis clinically and/or abnormal cerebrospinal fluid.

The report is based on the clinical records of the patients. All of the patients were seen by one or more of the study physicians. The incubation period was defined as the interval between the last contact with pig and the onset of clinical symptoms and was deduced from patients who left the area in a subsequent voluntary evacuation. The patients were managed in two dedicated wards. They were given general supportive therapy, anticonvulsants and other agents as necessary. The indications for ventilation were: Glasgow coma scale (GCS) score <8, rapidly deteriorating GCS score or inability to protect airway because of seizure. Patients were treated with inotropic agent(s) if they had persistent hypotension despite adequate volume. Ribavirin, a nucleoside analogue antiviral drug was used in 65% of the patients.

For serology, the CSF and serum samples were tested with an IgM-capture enzyme-linked immunoabsorbant assay (ELISA) for antibodies against Hendra virus antigen. The antigens were inactivated by cobalt irradiation.

Univariate analyses were performed to correlate specific clinical features or laboratory findings with the outcome. For contingency tables, chi square tests with Yate's correction when necessary, were used. When the numbers were small the two-tailed Fisher's exact test was used. For unpaired non-parametric variables, Kruskal-Wallis statistics were used. Unpaired parametric variables were tested with analysis of variance. Where multiple comparisons for parametric variables were necessary, we used analysis of variance with Bonferroni's correction. The prognostic factors for outcome were analysed with multivariate logistic regression. All values below 0.05 were considered statistically significant. All values of relative risks (RR) were also expressed in 95% confidence interval.

RESULTS

Demographic characteristics

The demographic and epidemiological characteristics are listed in Table 1. The mean age was 38 ± 14 years (4-75). As for the 10 patients who have other occupations, there was each a coffee-shop operator, carpenter, oil palm seller, farmer, retired pig farm worker, clerk, housemaid, housewife, a student and a 4.5 year old child. All the patients had direct contact or were in close proximity to pigs in the course of their daily life.

Clinical and laboratory features

The incubation period based on the 49 patients who left the pig farm before the onset of symptom was: 10 ± 8.7 days (1-32).

Table 1: Demographic features of patients with Nipah encephalitis

Characteristics		No. of patients (%) (N=103)	
Gender	Male	91	(88)
	Female	12	(12)
Race	Chinese	60	(58)
	Indian	25	(24)
	East Malaysian	4	(4)
	Migrant	14	(14)
	Indonesian	10	(10)
Occupation	Nepalese	4	(4)
	Pig farmers	41	(40)
	Hired workers	39	(38)
	Truck drivers	8	(8)
	Culling team members	3	(3)
	Abattoir workers	2	(2)
	Others (see text)	10	(10)

Table 2: Symptoms at presentation of patients with Nipah encephalitis

Symptom	Percentage (N = 103)
Fever	97
Headache	88
Chills or rigors	51
Myalgia	47
Dizziness	39
Vomiting	36
Flu-like symptoms	29
Anorexia	27
Seizure	27
Sore throat	21
Diarrhoea	21
Fatigue, malaise or lethargy	19
Nausea	16
Abdominal pain	8
Arthralgia	7
Focal neurological symptoms	5
Dyspnoea	2
Chest pain	2
Constipation	2
Vertigo	2
Urinary symptoms	2

There were four patients who had a fixed period of exposure. These were the patients who went into the area, contracted the disease, and subsequently left the outbreak area. In these patients, the interval from the time they left the area until the onset of symptoms was 2.3 ± 3.2 days (0-7). The interval from the time they moved into the area until the onset of symptoms

Table 3: Clinical signs of patients with Nipah encephalitis

Signs	Percentage (N = 102)
Drowsiness	85
Confusion	69
Hyporeflexia	59
Myoclonus	54
Diaphragmatic muscle	20
Limbs muscles	17
Facial muscles	3
Diaphragmatic and limbs muscles	7
Limbs and facial muscles	3
Diaphragmatic and facial muscles	2
Diaphragmatic, limbs and facial muscles	2
Tachycardia (heart rate > 120 bpm)	53
Hypertension	52
Ptosis	30
Sweating (profuse or segmental)	27
Nystagmus	25
Hypotonia	25
Dysconjugate eye movement	16
Babinski's sign	16
Paralysis	15
Neck stiffness	12
Cranial nerve(s) palsy	9
Cerebellar signs	3

was 16.5 ± 19.4 days (2-45). The mean incubation period of these four patients was 9.4 days.

For most patients, the presenting symptoms mimic benign viral illness with some of them having respiratory and abdominal symptoms (Table 2). The focal neurological symptoms seen in the five patients were: two with diplopia, one each with

blindness, ataxia and dysarthria. Table 3 lists the clinical signs. As for the myoclonus, they occurred with the frequency of about 2 Hz. Of the patients who had segmental sweating, some were unilateral, all were in the upper part of the body.

Although the most prominent manifestations originated from the central nervous system, other organs were involved as evident by the abnormal laboratory and radiological findings, as listed in Table 4. Chest x-rays were taken just before or immediately after intubation in 42 patients. Eight patients (7.8%) were found to have Syndrome of Inappropriate Antidiuretic Hormone in their recovery phase, with hyponatraemia and natriuresis without renal failure.

Sixty-two patients (61%) were ventilated. The interval between the onsets of symptoms to intubation was 5.8 ± 4.2 days. The patients were ventilated for a mean period of 6.6 ± 5.4 days. The majority of the ventilated patients developed dysautonomia, which were: hypertension (74%), tachycardia (71%), sweating, and hyperglycaemia (58%). Lymphopaenia and thrombocytopenia occurred at about the same time as ventilation; (onset of symptom to lymphopaenia: 5.8 ± 4.8 days, onset of symptom to thrombocytopenia: 6.0 ± 4.3 days). Dysautonomia was noted two to three days later; and that of raised aspartate transaminase after another two days. There was, however, substantial overlap between the occurrence of these clinical and laboratory changes.

The Hendra serology was positive in 91 patients, however when compared with the patients with negative serology, there was no difference in clinical features, laboratory results, proportion being ventilated or mortality.

Outcome

The mortality was 41%. The interval between the onsets of symptom to death was 10 ± 6.8 days. The preterminal events were autonomic derangements with eventual hypotension unresponsive to triple inotropes (dobutamine, dopamine and high dose adrenaline or noradrenaline infusion). When the surviving

Table 4: Summary of laboratory and radiological findings of patients with Nipah encephalitis

Laboratory features	Percentage (N)	Means \pm SD (range)
Abnormal cerebrospinal fluid *	83 (54)	Protein: 1.3 ± 1.1 (0.32-7.0) g/dl Sugar: 5.5 ± 4.9 (3.6-34.4) mmol/l White cell: 61 ± 101 (0-384)/mm ³
Positive sera Hendra IgM serology	81 (91)	
Positive CSF Hendra IgM serology	58 (31)	
Thrombocytopenia (< 150,000/ μ l)	66 (102)	139000 ± 55100 (41000-331000) / μ l
Elevated alanine transaminase (> 65 IU/L)	61 (76)**	119 ± 120 IU/l
Elevated aspartate transaminase (> 37 IU/L)	60 (76)**	108 ± 112 IU/l
Lymphopaenia (< 1000 lymphocytes/ μ l)	60 (102)	1050 ± 579 (279-3351)/ μ l
Chest x-ray changes	24 (42)	
Left upper lobes alveolar consolidation	10 (42)	
Bilateral upper lobes alveolar consolidation	2 (42)	
Lower lobes alveolar consolidation	7 (42)	
Reticular changes	5 (42)	

* Cerebrospinal fluid is defined as abnormal if the white cell count is > 5 /mm³ or protein > 0.45 g/dl

** One patient with concomitant acute alcoholic hepatitis was excluded in analysis.

Table 5: Prognostic factors of Nipah encephalitis

Prognostic factors*	Mortality in the presence of prognostic factor percentage	Mortality in the absence of prognostic factor percentage	Relative risks (95% CI)		
	(no. of patients/N)	(no. of patients/N)			
Tachycardia	69 (38/55)	8 (4/48)	3.3	(2.1 < RR < 4.9)	P < 0.001
Hyperthermia	79 (23/42)	14 (9/61)	5.2	(2.8 < RR < 9.6)	P < 0.001
Diastolic hypertension	84 (33/47)	16 (9/56)	6.0	(3.0 < RR < 12)	P < 0.001
Systolic hypertension	64 (36/57)	13 (6/46)	2.6	(1.8 < RR < 3.7)	P < 0.001
Hyperglycaemia	77 (31/41)	17 (10/60)	4.9	(2.6 < RR < 9.2)	P < 0.001
Sweating	70 (19/27)	30 (23/70)	2.3	(1.5 < RR < 3.5)	P < 0.001
Need of inotrope(s)	84 (31/37)	17 (11/64)	4.9	(2.8 < RR < 8.5)	P < 0.001
Ventilation	58 (36/62)	15 (6/41)	4.0	(1.8 < RR < 8.6)	P < 0.001
Antiepileptic agent used	64 (29/45)	22 (13/58)	2.9	(1.7 < RR < 4.9)	P < 0.001
Myoclonus	54 (30/56)	26 (12/47)	2.1	(1.2 < RR < 3.6)	P = 0.007
Thrombocytopenia	57 (30/53)	25 (12/50)	1.9	(1.3 < RR < 2.7)	P = 0.008
Raised aspartate transaminase	54 (14/25)	24 (12/51)	2.4	(1.2 < RR < 4.5)	P = 0.009
Lymphopenia	51 (31/61)	25 (11/42)	1.5	(1.1 < RR < 2.1)	P = 0.006
Diabetes mellitus	86 (6/7)	38 (36/96)	2.3	(1.5 < RR < 3.4)	P = 0.018
Age > 40 years	55 (27/50)	29 (15/53)	1.8	(1.2 < RR < 2.7)	P = 0.017

* On the need of inotropic agents and ventilation, see text for definition. Hyperglycaemia is defined as peak random plasma sugar of ≥ 11.1 mmol/l. Tachycardia is defined as peak heart rate ≥ 120 beats per-minute. Hyperthermia is defined as peak temperature $\geq 40^\circ\text{C}$. Systolic hypertension is defined as peak systolic blood pressure ≥ 160 mmHg. Diastolic hypertension is when the diastolic component of the peak systolic hypertension is ≥ 100 mmHg. Thrombocytopenia is defined as trough platelet count $< 133,000/\mu\text{l}$. Elevated aspartate transaminase is peak level ≥ 100 IU/l. Lymphopenia is trough lymphocytes count < 1000 cells/ μl . The average patient is taken of having a relative risk of 1.0 and mortality of 41%.

patients were last seen five months since the outbreak, some 40% recovered fully while 19% had residual neurological deficits which were: cerebellar signs (6.8%), tetraparesis (4.9%), cranial nerve palsies (3.9%), monoparesis (1.0%), peripheral nerve lesions (2.9%) and higher mental function deficits (2.9%). Of the four patients with cranial nerve palsies, two had facial nerve palsy, one each had unilateral sensorineural deafness and diplopia. Of the three patients with peripheral nerve lesions, one each had ulnar nerve palsy, foot drop, and digital numbness. Of the three patients with higher mental deficits, one each had medial temporal syndrome (hyperphagia, inappropriate sexual behaviour), global dysphasia and vegetative state. As for the functional status, one patient was in persistent vegetative state, two have marked disabilities and are dependent on caregivers, while four have mild disabilities and are independent in their activities of daily living.

Table 5 lists the prognostic factors for mortality. On logistic regression analysis, tachycardia ($p=0.025$), high fever ($p=0.039$) and hypertension ($p=0.045$) were independently associated with poor outcome.

DISCUSSION

Pig farming in the Bukit Pelanduk area started almost 70 years ago. The industry had largely remained a family business. Often the owner and his family took care of the animals with assistance from a few migrant workers, mainly from Bangladesh, Indonesia and Nepal. Bukit Pelanduk and its neighbouring areas had developed into the biggest pig farm industry centre in South East Asia. There were estimated a million pigs at the time of the

outbreak.⁷ The pigs were exported to Singapore as well as for home market.

The patient characteristics of mainly adult Chinese males who worked with live pigs, full time or part-time suggested that it was a zoonotic disease from pigs.^{7,8,16,17} Animal studies have shown a moderate to severe interstitial pneumonia with immunohistochemical staining showing high concentration of viral antigen in the endothelial cells of blood vessels, as well as in the cellular debris in the lumen of the upper respiratory tract. The disease could thus spread from pig to man through infected secretions by direct body contact or via respiratory droplets at close range.^{7,16-18} The disease initially affected 27 pig farmers in Perak at the north with 15 mortality. When the encephalitis occurred in Perak, the government imposed restriction on the transportation of pigs across state border. Some farmers had disregarded this. This may be the cause of the spread of the disease.¹⁸

The estimated mean incubation period was short at 10 days, and the longest was 32 days. This may be an underestimation as it was based on the time of last exposure. In one of the patients with a fixed period of exposure time, the symptoms started two days after entering the area suggesting that the incubation period could be as short as two days. Many of the patients also gave the history of the pigs falling ill around Chinese (lunar) New Year on the 16th and 17th of February 1999. The first few patients had the onset of symptoms on the 18th to the 22nd of February 1999, again suggesting a relatively short incubation period.

The patients commonly complained of symptoms that mimic benign viral illness with fever, headache, chills, rigors, and myalgia probably due to the initial viraemia. About a quarter of the patients had sore throat and an equal number had flu-like

symptoms with cough suggestive of respiratory tract involvement. Pathological studies have shown vasculitic changes in the lung.⁵ Some had gastrointestinal symptoms of anorexia, nausea, vomiting, diarrhoea and abdominal pain. These could be due to nervous or direct gastrointestinal involvement.

Many of the patients subsequently developed drowsiness, confusion and focal neurological signs. The conscious state deteriorated rapidly with ventilation required in 61% of the patients. The interval between the onset of symptom to intubation was 5.8 days. The common occurrence of coma, diaphragmatic myoclonus, autonomic changes with tachycardia, hypertension, hyperthermia, profuse and segmental sweating, ptosis and nystagmus suggested prominent involvement of the brainstem, upper spinal cord and hypothalamus. Disseminated microinfarction in the brain secondary to vasculitis-induced thrombosis has been the main pathological finding.⁵ The neurological features could be partly due to the widespread microinfarction. There is also evidence of direct neuronal involvement with neuronal inclusion body and positive immunohistochemical staining of neurons.^{3,5,6} The myoclonus, particularly the diaphragmatic myoclonus which was a characteristic feature of the illness, would be consistent with direct neuronal involvement.⁸ The previously demonstrated association between CSF virus isolation and mortality also support direct neuronal invasion being important in the pathogenesis of severe disease.¹⁰ The meningism which was seen in only 12% of the patients was consistent with the CSF examination, which was normal in 17% of the cases. Histologically, meningitis was generally mild.⁵

Paton et al³ reported three of their eleven patients who were abattoirs workers in Singapore presented with atypical pneumonia, one later had evidence of cerebral involvement. Although chest radiograph abnormalities were noted in 24% of our cases, none had primary lung disease. This is similar to the finding from the University Malaya Medical Centre, which is the other major treatment centre for the encephalitis.⁸ These indicate that the virus caused a predominantly neurological disease. Pathologically, although organs including the lung, heart and kidney were affected, the brain was the most severely affected organ.⁵

The mortality was high at 41%. The mean duration of illness from onset of symptoms to death was 16 days. Goh et al⁸ reported that tachycardia and an abnormal doll's-eye reflex were associated with poor outcome, suggesting a severe brainstem involvement in the fatal cases. We found that in addition to this, hypertension and high fever were also associated with mortality. The association of hypertension and high fever with mortality is also consistent with severe brainstem and hypothalamic involvement in the fatal cases. The association of thrombocytopenia, raised aspartate transaminase and hyperglycemia with mortality is probably reflective of non-specific changes of the very sick patients.

Although the mortality was high, for the patients who survived, the outlook was good. Most of the 23 patients (19%) with residual neurological deficits were mild. Most were able to independently carry out their activities of daily living. The outcome is better than that of Japanese encephalitis, another encephalitis related to pig farming.¹⁹

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