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Nipah Encephalitis: A report of 18 patients from Kuala Lumpur Hospital

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Abstract

Nipah virus, a previously unknown paramyxovirus, was identified as the cause of the encephalitis outbreak among pig-farmers in Malaysia. We describe the clinical features and results of investigation in 18 patients seen in the Kuala Lumpur Hospital. Twelve patients were Malaysians and 6 patients were foreign workers. The majority were young adult males who have direct body contact with pigs. Incubation period ranged from 2 days to one month. Prodromal symptoms were nonspecific, followed by drowsiness and confusion after a few days. Most common neurological signs were coma, hyporeflexia or areflexia, segmental myoclonus, gaze palsy and limb weakness. Notable laboratory findings include thrombocytopaenia and abnormal cerebrospinal fluid analysis. Of the 18 patients, 17 required ventilation of whom 11 died (61%). Another patient died of respiratory infection 4 months after discharge. Of the survivors, only one patient recovered with no neurological deficits.
Conclusions: Infection with Nipah virus causes fulminant encephalitis with high mortality and morbidity.

INTRODUCTION

From September 1998 to May 1999, an epidemic of fatal encephalitis occurred among pig-farmers in Malaysia.[1-6] A smaller outbreak occurred among abattoir workers in Singapore.[7,8] The encephalitis was initially thought to be Japanese encephalitis, but later was shown to be due to Nipah virus, a previously unknown paramyxovirus.[3,9] The Nipah virus was closely related to the Hendra virus which caused disease in horses and humans in Australia in 1994.[10,11] During the epidemic, most of the patients were seen in the Seremban Hospital[12], University Malaya Medical Centres[3,4], Kuala Lumpur Hospital and Ipoh Hospital. This is a report of the 18 patients seen in the Kuala Lumpur Hospital. Kuala Lumpur Hospital is a national tertiary referral medical centre about 70 km north of Bukit Pelanduk. Bukit Pelanduk was the largest outbreak area during the Nipah encephalitis epidemic.

METHODS

All cases suspected of Nipah encephalitis admitted to the neurology and the intensive care wards of the Kuala Lumpur Hospital were studied. The diagnosis of Nipah encephalitis was based on the following criteria: lived, worked, visited the outbreak area or has exposure to pigs from the outbreak area; clinical evidence of encephalitis; and presence of Hendra IgM antibody in serum or CSF or Nipah virus antigen in brain biopsy material. The method of serology testing using enzyme-linked-immunosorbent assay has been previously described.[3] Patient data were abstracted using standardised data collection form, stored and analysed using Epi-info version 6.04.

RESULTS

Demographic features

Table 1 lists the demographic, clinical & laboratory features of the patients. As shown, the mean age was 37 years (range: 14-64 years). There were 9 Chinese (50%), 2 Indians (11%), one Malay (6%), and 6 immigrant workers (33%) from Nepal, Indonesia, Myanmar and Bangladesh. Eleven patients were males (61%) and 7 were females (39%). Ten patients (56%) were pig-farm owners or workers. The other 8 patients (44%) were in the outbreak area or had other exposure to the pigs. Four of the patients (22%) had no direct body contact with the pigs. The onset of symptom was between 25th February and 27th May of 1999.

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Table 1: Demographic, clinical and laboratory features of the patients with Nipah encephalitis

Case	Age (years) /Sex	Nationality/Race	Occupation and contact with pigs	Days of illness before admission	Dominant neurological features	Serum Hendra 1gM serology	CSF Hendra 1gM serology	Blood platelet count	Outcome after admission
1.	26, Male	Malaysian Chinese	Butcher	5	Generalised seizure, myoclonus tetraparesis, hyporeflexia, coma	+	-ve	↓	Died day 16
2.	33, Male	Malaysian Chinese	Pig-Farm owner	2	Generalised seizures, myoclonus gaze palsy, hyporeflexia, coma	+	NA	↓	Died day 8
3.	14, Female	Malaysian Chinese	Student, visitor to pig farm*	6	Confusion, drowsiness, areflexia	+	+	Normal	Recovered
4.	51, Female	Malaysian Chinese	Pig-farm worker	5	Gaze palsy, myoclonus, areflexia, coma	+	-ve	↓	Died day 1
5.	37, Male	Malaysian Chinese	Pig-farm owner	4	Generalised seizure, hyporeflexia myoclonus, coma	NA	-ve *	↓	Died day 4
6.	32, Female	Malaysian Chinese	Pig-farm worker	9	Gaze palsy, generalised seizure myoclonus, areflexia, tachycardia	+	NA	↓	Died day 2
7.	28, Male	Malaysian Chinese	Pig-farm worker	3	Hyporeflexia, myoclonus, gaze palsy, tetraparesis, coma	+	+	↓	Partial recovery
8.	39, Male	Nepalese	Pig-farm worker	4	Gaze palsy, hyporeflexia, myoclonus, tetraparesis, coma	+	+	↓	Died day 35
9.	49, Female	Malaysian Chinese	Pork-ball maker at a slaughter house	3	Myoclonus, hyporeflexia, coma	+	NA	↓	Died day 5
10.	47, Female	Malaysian Indian	Factory worker, play with piglet	13	Arthritis, myoclonus, areflexia, tetraparesis, coma	+	-ve	↓	Partial recovery
11.	39, Male	Malaysian Indian	Pig-Farm worker	4	Gaze palsy, bilateral ptosis, tetraparesis, myoclonus areflexia	+	NA	↓	Poor recovery died 4 months after discharge
12.	28, Male	Nepalese	Butcher, helped in the disposal of carcasses	1	Myoclonus, areflexia, coma, disinhibition, Parkisonism	+	NA	Normal	Partial recovery
13.	37, Female	Indonesian	Pig-Farm worker	4	Gaze palsy, areflexia, myoclonus, coma, tachycardia	+	-ve	↓	Died day 7
14.	46, Male	Malaysian Malay	Driver, passed outbreak area regularly*	1	Partial seizure, gaze palsy, bilateral ptosis, areflexia, myoclonus	+	NA	Normal	Partial recovery
15.	26, Male	Nepalese	Pig-Farm worker	7	Generalise seizure, bilateral ptosis gaze palsy, areflexia, myoclonus	+	-ve	Normal	Died day 15
16.	64, Female	Malaysian Chinese	Factory worker at outbreak area*	7	Gaze palsy, bilateral ptosis myoclonus, hyporeflexia, coma	+	-ve	↓	Died day 31
17.	40, Male	Myanmese	Pig-Farm worker	7	Myoclonus, areflexia, coma	+	NA	↓	Died day 4
18.	29, Male	Bangladeshi	Factory worker at outbreak area*	3	Hyporeflexia, myoclonus, tetraparesis, coma	+	NA	↓	Partial recovery

* Has no direct body contact with pigs.
** diagnosis confirmed by positive immunohistochemistry for Nipah antigen.
NA = not available; ↓ = low

Clinical features

The incubation period, defined as the time between last contact with pigs or outbreak area to onset of symptoms could be determined in only 6 patients. These patients fell ill after a mean of 13 days (2, 6, 9, 12, 21 and 30 days).

The initial symptoms were often non-specific. The prodromal symptoms consisted of fever (94%), headache (67%), dizziness (44%), vomiting (39%), lethargy (33%), chills and rigors (33%), myalgia (22%), cough (17%), and arthralgia, diarrhoea in one patient each. One other patient had knee arthritis requiring admission to orthopedic ward initially.

Neurological symptoms occurred as the initial symptom in one patient. In 16 (89%) other patients, neurological symptoms appeared within a week. In one other patient, the neurological symptoms did not appear until the 19th day of fever. The dominant neurological features of the individual patients are as listed in table 1. Table 2 lists the frequency of the various neurological signs. For the segmental myoclonus seen in 17 patients, in 8 patients the myoclonus involved several muscle groups either simultaneously or sequentially. Common sites of myoclonus were the limbs, larynx, diaphragm, neck and face. Of the 7 patients with tetraparesis, 4 patients survived. Of the survivors, 3 patients recovered to be able to walk with minimal assistance at the time of discharge from Hospital and the other patient was wheelchair-bound. The autonomic dysfunction seen in 6 patients consisted of labile blood pressure in 5 patients, persistent hyperpyrexia in one patient and tachycardia. The 3 patients with cerebellar dysfunction had nystagmus, dysdiadochokinesia and intention tremor.

Neurological deterioration may occur quite fast and coma can develop within few hours. In the 17 patients (94%) who required ventilation because of deepening coma and inability to maintain airways, 11 patients (65%) were intubated within one week of illness, 4 (22%) in the 2nd week, and one each in the 3rd and 4th weeks. The mean interval from onset of illness to death was 16 days (median, 10 days; range, 4-39 days). Fatal cases were on ventilator for an average of 9 days (median, 6 days; range 1-34 days) before death. Ten of the 11 deceased patients had minimal central nervous system activity preceding

Table 2: Neurological signs of the patients with Nipah encephalitis

Signs	Number of patients (%)
Hyporeflexia	18 (100)
Coma requiring ventilation	17 (94)
Segmental myoclonus	17 (94)
Gaze paralysis	9 (50)
Limb weakness*	8 (44)
Autonomic dysfunction	6 (33)
Bilateral ptosis	4 (22)
Seizure	4 (22)
Neck stiffness	3 (17)
Cerebellar signs	3 (17)
Diabetes insipidus	3 (17)
SIADH#	
Parkinsonism**	1 (6)
Disinhibition**	1 (6)
Hyperphagia**	1 (6)
Bulbar palsy	1 (6)
Babinski sign	1 (6)

* 7 patients had tetraparesis and one patient had monoparesis.
** The Parkinsonism, disinhibition and hyperphagia occurred in a single patient.
# SIADH - Syndrome of Inappropriate antidiuretic hormone secretion

death. The other patient (Case 15) although in need of ventilation, had good brainstem reflexes but died suddenly of hypotension secondary to autonomic dysfunction. Three patients (17%) developed supraventricular tachycardia and cardiogenic shock prior to death (cases 6, 8, 13). Ten patients (56%) received ribavirin therapy.

Laboratory Investigations

Thrombocytopaenia occurred in 14 patients (78%), usually at the nadir of the illness. Median platelet count was 105,000/mm^3 (range: 35,000-276,000/mm^3). Electrolytes were within normal limits, except for 2 patients with hyponatraemia from SIADH (lowest values were 118 and 124 mmol/L respectively). All patients had normal chest x-ray on admission.

Cerebrospinal fluid examination was carried out in 15 patients of whom 14 showed abnormality in at least one parameter. Eleven patients (78%) had high protein and raised cell counts, 2 patients (14%) had raised cell count only and one patient (7%) had elevated protein only. The mean cerebrospinal fluid sugar was 4.0 mmol/l (range: 0.4-7.7 mmol/l); the mean cerebrospinal fluid protein was 0.7 g/l (range: 0.2-2.0 g/l) and the mean white cell count was 75/mm^3 (range: 0-415/mm^3). Nine of the 13 patients with cerebrospinal fluid pleocytosis showed lymphocyte predominant picture. All the 17 patient had positive Serum Hendra IgM serology. Three out of 10 patients (30%) had positive cerebrospinal fluid Hendra IgM serology.

Electroencephalogram was done in 11 patients and 10 showed diffuse slowing of background activities. Additionally 3 patients had focal sharp waves over frontal, temporal and central regions. One other record showed hypersynchronous fast activities related to midazolam.

Computed tomography of the brain showed multiple hypodense lesions in 3 patients and no focal lesion in the remaining 12 patients. MR imaging of the brain was done in 6 patients and all were abnormal. Four patients had multiple discreet hyperintense lesions on T2-wighted sequence, while 2 other patients have large confluent lesions which extended into the grey matter.

Outcome

Eleven patients died during the acute encephalitis with mortality of 61%. Contigency table analysis with Fisher's exact test showed no significant association between mortality and any of the following variables: age, myoclonus, autonomic dysfunction, seizure, Glasgow Coma Scale on admission, thrombocytopaenia and ribavirin therapy.

Of the 7 patients who survived the acute encephalitis, one patient made full recovery, was able to resume her study and has remained well. The other 6 patients have significant neurological deficits consisting of cognitive impairment in all the patients, cerebellar signs in 2 patients, generalised myoclonus in one patient, Parkinsonism and hyperphagia in another patient. One patient died from chest infection 4 months after discharge, 8 months after onset of illness. At one year of follow-up, of the 6 patients, 3 patients continued to have neurological deficits, one patient remained well while 2 patients returned to Bangladesh and Nepal respectively and were lost to follow-up.

DISCUSSION

The outbreak of Nipah encephalitis occurred in 4 waves. The first wave was Ulu Piah, Tambun and Ampang, near Ipoh Town in Perak State. The second wave occurred in Sikamat in Negri Sembilan State, 200km south of Tambun. The third wave, which was the largest, affected areas around Bukit Pelanduk in the same state, and the neighbouring Sepang in the Selangor State. The 4^{th} wave was in Sungei Buloh village in Selangor State. Figure 1 shows the geographical location of the outbreak areas. The demography of the illness, affecting mainly male pig farm workers is consistent with an infection from the pigs. The 4 patients in our series who did not have direct body contact with pigs shows that the infection may also be transmitted by respiratory droplets at close range.[4,13]

The mean incubation period of 13 days determined in the 6 patients is in the same range as earlier reports.[4,12] The incubation period was two weeks or less in 92% of patients from University Malaya Medical Centre. [4] The mean incubation period estimated from the patients in Seremban Hospital was 10 ± 8.7 days.[12] The non-specific symptoms during presentation is also similar to the earlier reports.[4,6,12] Although arthralgia was also noted in the report from Seremban Hospital[12], arthritis as was seen in one of our patients has not been noted earlier. Paton et al[8] reported three of their 11 patients in Singapore presented with atypical pneumonia, one later had evidence of cerebral involvement. All our patients had normal chest x-ray on admission. The absence of primary pneumonic

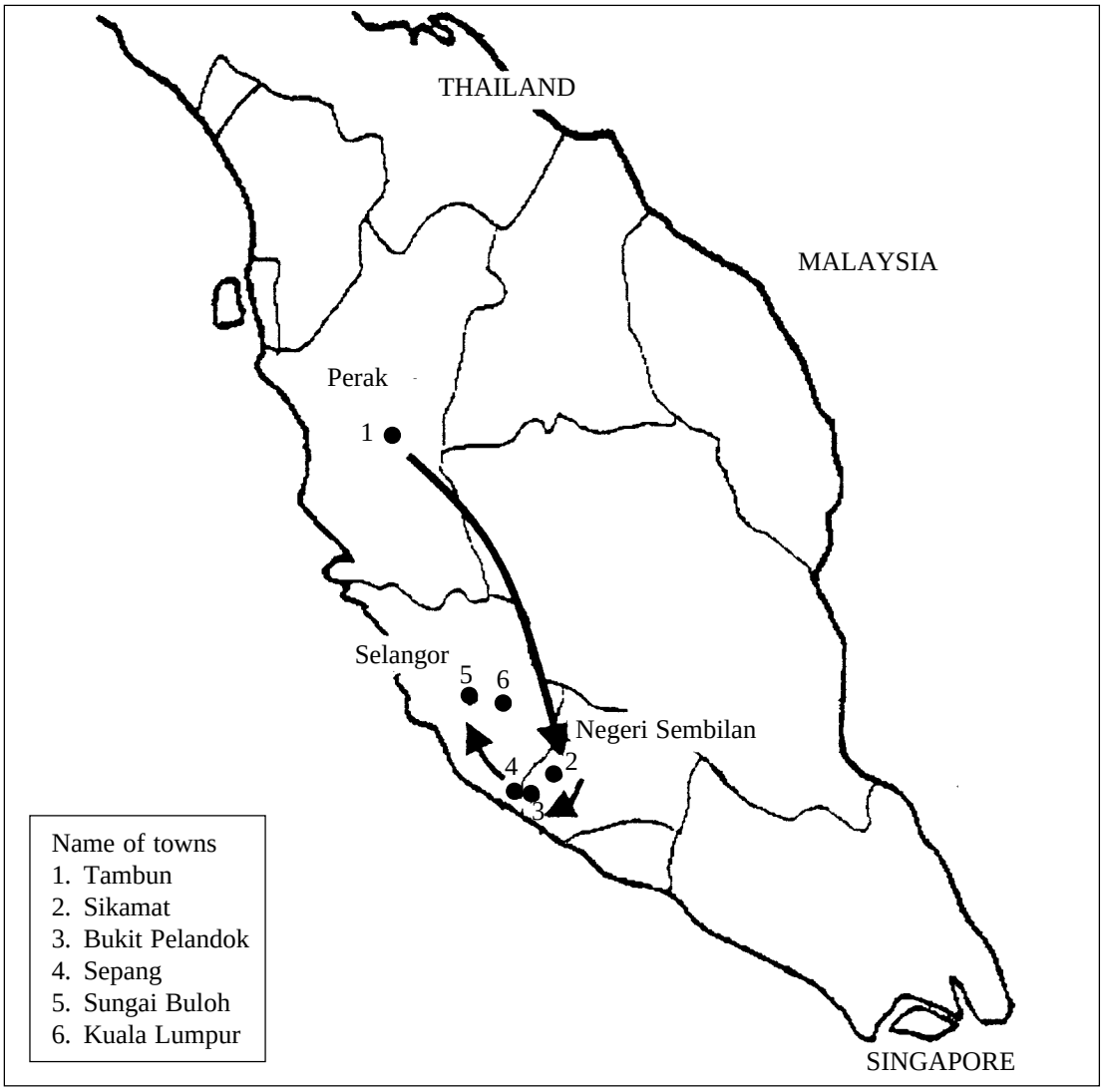

Figure 1: Map of Malaysia showing spread of Nipah encephalitis outbreak among neighbouring states

involvement has also been noted in the reports from University Malaya Medical centre[4] and Seremban Hospital.[12]

The common occurrence of rapidly developing coma, gaze paresis, cranial nerve palsies, autonomic and vasomotor dysfunction are consistent with prominent brainstem involvement.[4] Distinctive neurological features were hyporeflexia or areflexia, segmental myoclonus, autonomic dysfunction, relatively absence of Babinski sign although limb paresis was not uncommon.[4,12] Autopsy findings of widespread vasculitis, thrombosis and microinfarcts in the brain could explain the neurological findings.[3] The distinctive neurological features is supportive of direct neuronal involvement.[3,4] The association between cerebrospinal fluid virus isolation and mortality also support direct neuronal invasion being important in the pathogenesis of severe disease.[14]

Earlier reports from University Malaya Medical Centre and Seremban Hospital have found association between thrombocytopenia and mortality, suggesting that thrombocytopenia may be a non-specific change of the very sick patients.[4,12] The cerebrospinal fluid changes is also consistent with the earlier reports.[4,12] Previous reports of MR imaging has emphasized the common occurrence of discrete high-signal-intensity lesions best seen in the fluid attenuated inversion recovery sequence, measuring 2-7 mm, occurring mainly in the subcortical and deep white matter as well as grey matter of the brain.[7,8,15] Two of our patients showed the less common

findings of larger confluent lesions in the subcortical white matter extending to the grey matter.

Analysis of various clinical and laboratory findings did not reveal any significant predictor of mortality. This is likely to be due to small sample size. Earlier reports have identified severe brainstem dysfunction, such as coma, abnormal doll's-eye reflex, abnormal pupils, hypertension, tachycardia, vomiting as significant risk factors of poor outcome. Other predictors of mortality are: myoclonus, thrombocytopaenia, high hepatic enzyme level[4,12], presence of Nipah virus in cerebrospinal fluid[14], and diabetis meilitus.[16] Ribavarin on the other hand, has a protective effect.[17]

The overall mortality at 67% is high. The mortality in the other treatment centres were: Seremban Hospital (41%)[12], University Malaya Medical Centre (32%)[4], and Singapore (9%).[8] The overall mortality for the outbreak involving 265 cases of encephalitis in Malaysia was 40%.[5]

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