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CLINICAL FEATURES OF NIPAH VIRUS ENCEPHALITIS AMONG PIG FARMERS IN MALAYSIA

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ABSTRACT

Background Between September 1998 and June 1999, there was an outbreak of severe viral encephalitis due to Nipah virus, a newly discovered paramyxovirus, in Malaysia.

Methods We studied the clinical features of the patients with Nipah virus encephalitis who were admitted to a medical center in Kuala Lumpur. The case definition was based on epidemiologic, clinical, cerebrospinal fluid, and neuroimaging findings.

Results Ninety-four patients with Nipah virus infection were seen from February to June 1999 (mean age, 37 years; ratio of male patients to female patients, 4.5 to 1). Ninety-three percent had had direct contact with pigs, usually in the two weeks before the onset of illness, suggesting that there was direct viral transmission from pigs to humans and a short incubation period. The main presenting features were fever, headache, dizziness, and vomiting. Fifty-two patients (55 percent) had a reduced level of consciousness and prominent brain-stem dysfunction. Distinctive clinical signs included segmental myoclonus, areflexia and hypotonia, hypertension, and tachycardia and thus suggest the involvement of the brain stem and the upper cervical spinal cord. The initial cerebrospinal fluid findings were abnormal in 75 percent of patients. Antibodies against Hendra virus were detected in serum or cerebrospinal fluid in 76 percent of 83 patients tested. Thirty patients (32 percent) died after rapid deterioration in their condition. An abnormal doll's-eye reflex and tachycardia were factors associated with a poor prognosis. Death was probably due to severe brain-stem involvement. Neurologic relapse occurred after initially mild disease in three patients. Fifty patients (53 percent) recovered fully, and 14 (15 percent) had persistent neurologic deficits.

Conclusions Nipah virus causes a severe, rapidly progressive encephalitis with a high mortality rate and features that suggest involvement of the brain stem. The infection is associated with recent contact with pigs. (N Engl J Med 2000;342:1229-35.)

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BETWEEN September 1998 and June 1999, there was an outbreak of febrile encephalitis in several pig-farming villages in Malaysia. More than 200 patients were admitted to hospitals nationwide, many of whom died.¹⁻³ The pig-farming industry was disrupted by the culling of many pigs to control the outbreak and the closing of farms. Several abattoir workers in neighboring Singapore were also affected.^{4,5} Japanese encephalitis, a viral encephalitis associated with pigs that is endemic in Southeast Asia, was initially suspected, but clinical and epidemiologic features suggested that a different disease was responsible.

The isolation of a new paramyxovirus, subsequently named Nipah virus, from cerebrospinal fluid specimens from several patients indicated that this was the etiologic agent.³ Preliminary studies of nucleotide sequencing revealed that this virus is closely related to, but not identical to, Hendra virus, which caused disease among horses and affected three patients in Australia.^{1,6,7}

We describe the clinical and laboratory features of patients with Nipah virus infection who were seen at the University of Malaya Medical Center, Kuala Lumpur, one of the two main hospitals to which patients were admitted during the outbreak.

METHODS

The patients were treated by a team of neurologists, infectious-disease physicians, and intensive care physicians. Clinical observations and base-line laboratory results were recorded prospectively. Cerebrospinal fluid was examined in nearly all patients, and electroencephalography and magnetic resonance imaging (MRI) of

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the brain, with a 1.5-tesla scanner (Siemens), were performed in some patients.

Isolation of virus was not attempted in all patients for fear of laboratory-acquired infection. When viral isolation was attempted, syncytial-cell formation on Vero cell cultures (American Type Culture Collection and certified cell line 81) several days after inoculation indicated the presence of the virus.³ Serum and cerebrospinal fluid samples were tested with an IgM-capture enzyme-linked immunosorbent assay (ELISA) and indirect IgG ELISA for antibodies against Hendra virus antigens.^{1,3} These tests were developed for use and found to be effective during the outbreak, pending the development of antibody tests that used Nipah virus antigens.

Because confirmatory tests (viral isolation or Nipah virus serologic tests) could not be readily performed, a case definition based on epidemiologic and clinical features was adopted. Patients were considered to have Nipah encephalitis if they came from areas known to be involved in the outbreak, had had direct or close contact with pigs or other infected animals, and had evidence of encephalitis. Encephalitis was defined by the presence of one of the following: clinical features (fever, headache, altered sensorium, or focal neurologic signs), abnormal cerebrospinal fluid findings (≥ 6 lymphocytes per cubic millimeter or a protein level of at least 0.45 g per liter in patients under 50 years of age and a level of at least 0.55 g per liter in patients who were 50 years of age or older), or characteristic findings on MRI of the brain. Patients with positive antibodies against Hendra virus antigens but no clinical or laboratory evidence of neurologic involvement were considered to have nonencephalitic Nipah virus infection.

Statistical analysis was performed with the χ^2 test or Student's t-test. The prognostic factors for outcome of the infection were analyzed by multivariate logistic regression.

RESULTS

Characteristics of the Patients

Between February 1999 and June 1999, a total of 110 patients were hospitalized with suspected Nipah virus infection. They were mainly from Bukit Pelanduk and neighboring villages in Negri Sembilan State south of Kuala Lumpur. Ninety-one (83 percent) fulfilled the criteria for Nipah encephalitis, and three additional patients had nonencephalitic Nipah infection. The mean age of the 94 patients with Nipah infection was 37 years (range, 13 to 68). The ratio of male patients to female patients was 4.5 to 1. The majority (83 percent) were ethnic Chinese, 14 percent were ethnic Indians, and 3 percent were of other races or ethnic groups. Eighty-seven (93 percent) were pig farmers or had occupations that involved direct contact with pigs, including working in an abattoir, selling animal vaccines, repairing pig cages, and involvement in pig-culling operations during the outbreak. Of these patients, 41 percent reported that the animals with which they had recently had contact had died after contracting an unusual respiratory tract illness. The period between the patient's last contact with pigs and the onset of illness ranged from several days to two months, and was two weeks or less in 92 percent of patients. Two patients had had direct contact with infected dogs (the dogs died of suspicious causes just before the patients became ill). The remaining patients (5 percent) lived close to but were not in direct bodily contact with pigs. More than half (56 percent) had affected family members,

TABLE 1. CLINICAL FEATURES AT PRESENTATION IN PATIENTS WITH NIPAH VIRUS INFECTION.

FEATURE	No. of PATIENTS (%) (N=94)
Fever	91 (97)
Headache	61 (65)
Dizziness	34 (36)
Vomiting	25 (27)
Reduced level of consciousness*	20 (21)
Nonproductive cough	13 (14)
Myalgia	11 (12)
Focal neurologic signs	10 (11)
Cerebellar signs	3 (3)
Segmental myoclonus	3 (3)
Cerebellar signs and segmental myoclonus	2 (2)
Rotatory nystagmus	1 (1)
Dysphasia	1 (1)

*A score of 15 on the Glasgow Coma Scale was considered to indicate a normal level of consciousness.

and 74 percent had been immunized against Japanese encephalitis virus.

Acute Clinical Features

Table 1 lists the main features at presentation. The mean duration of fever before admission was 3.5 days (range, 1 to 14). The disease predominantly affected the nervous system. The neurologic features are summarized in Table 2. Fifty-two patients (55 percent) had a reduced level of consciousness, as evidenced by a score of less than 15 on the Glasgow Coma Scale; the mean score at nadir (defined as the worst conscious level or the need for mechanical ventilation) was 7.5. The mean duration of the illness from the onset of symptoms to the nadir was 6.9 days (range, 3 to 31). Patients with a reduced level of consciousness had prominent signs of brain-stem dysfunction, including abnormal doll's-eye reflex, pinpoint pupils with variable reactivity, and prominent vasomotor changes consisting of hypertension and tachycardia, which suggested involvement of the medullary vasomotor center. Seizures occurred in 23 percent of all patients, and all but one of these patients had generalized tonic-clonic seizures; that patient had focal motor seizures with secondary generalization. No patient had status epilepticus. Segmental myoclonus, characterized by focal, rhythmic jerking of the muscles, was present in 32 percent. Eight patients had cerebellar dysfunction, and three had severe postural tremor of both arms.

Absent or reduced tendon reflexes with hypotonia were seen in 56 percent of patients. This condition was more common in patients with a reduced level of consciousness than in those with a normal level

TABLE 2. NEUROLOGIC CHARACTERISTICS OF PATIENTS DURING THE COURSE OF NIPAH VIRUS INFECTION.

CHARACTERISTIC	ALL PATIENTS (N=94)	PATIENTS WITH NORMAL LEVEL OF CONSCIOUSNESS (N=42)*	PATIENTS WITH REDUCED LEVEL OF CONSCIOUSNESS (N=52)*
Absent or reduced reflexes	53 (56)	11 (26)	42 (81)
Abnormal pupils	49 (52)	1 (2)	48 (92)
Tachycardia (heart rate >120/min)	37 (39)	0	37 (71)
Hypertension (blood pressure >160/90 mm Hg)	36 (38)	3 (7)	33 (63)
Abnormal doll's-eye reflex	36 (38)	0	36 (69)
Segmental myoclonus			
Overall	30 (32)	1 (2)	29 (56)
Diaphragm	26 (28)	1 (2)	25 (48)
Arms	13 (14)	0	13 (25)
Legs	9 (10)	0	9 (17)
Anterior muscles of neck	8 (9)	0	8 (15)
Facial muscles	1 (1)	0	1 (2)
Meningism	26 (28)	9 (21)	17 (33)
Seizures	22 (23)	0	22 (42)
Nystagmus	15 (16)	1 (2)	14 (27)
Cerebellar signs	8 (9)	0	8 (15)
Bilateral ptosis	4 (4)	2 (5)	2 (4)
Bilateral postural tremor	3 (3)	0	3 (6)
Dysarthria	3 (3)	1 (2)	2 (4)
Dysphasia	2 (2)	1 (2)	1 (2)

*A score of 15 on the Glasgow Coma Scale was considered to indicate a normal level of consciousness.

(81 percent vs. 26 percent). Nerve conduction studies were performed in five patients with areflexia during the acute phase (from the 10th to 20th day) of their illness. Two patients had normal results. In the other three patients, late responses (F wave and H wave) were absent; in one of these patients, who had diabetes mellitus, sensory nerve responses were also absent. In 10 comatose patients, a distinct pattern of recovery was observed, in which flaccid tetraplegia and areflexia persisted while cranial motor function and cognition improved, mimicking the locked-in syndrome. In eight patients, limb power subsequently recovered and reflexes returned. Four were able to walk independently. In five of these eight patients, transcranial magnetic stimulation of the motor cortex was carried out. Motor evoked potentials were absent in only one patient, who was the only patient in whom pyramidal signs developed during recovery.

All other systems were normal in all patients on admission. There was a history of major medical problems in 12 percent of the patients, including hypertension, diabetes mellitus, gout, ulcerative colitis, and gastritis. However, none of these conditions caused clinically significant morbidity. The complications in severely ill patients included systemic sepsis (24 percent), bleeding from the gastrointestinal tract (5 percent), renal impairment (4 percent), hemothorax from

insertion of a central catheter (2 percent), and pulmonary embolism (1 percent). Acute atrial fibrillation developed in two comatose patients. Echocardiography in both patients showed normal myocardial function.

Laboratory Investigations

Thrombocytopenia (defined as a platelet count of less than 140,000 per cubic millimeter) was found in 30 percent of patients and leukopenia (defined as a white-cell count of less than 4000 per cubic millimeter) in 11 percent. Blood urea, creatinine, and electrolyte levels were normal in all patients. Elevated levels of alanine aminotransferase (>65 U per liter) were found in 33 percent of patients, and elevated levels of aspartate aminotransferase (>37 U per liter) were found in 42 percent of patients. In 6 percent of patients, the chest radiographs were abnormal, with increased focal markings over the lung fields and, in one patient, mild basal atelectasis. All of these patients had primarily neurologic features at presentation, and only one had cough.

Cerebrospinal fluid examination was carried out in 92 patients (Table 3). The two patients who declined to undergo lumbar puncture had clinical encephalitis, and one of them died. The results of initial and repeated examinations were abnormal (as indicated by elevated white-cell counts, elevated protein

TABLE 3. RESULTS OF CEREBROSPINAL FLUID EXAMINATION IN PATIENTS WITH NIPAH VIRUS INFECTION.

EXAMINATION	NO. OF PATIENTS	DAY OF ILLNESS*	WHITE-CELL COUNT*	PROTEIN*	GLUCOSE*	PRESSURE*	PATIENTS WITH ABNORMAL RESULTS		
							TOTAL	ELEVATED PROTEIN LEVELS ONLY	ELEVATED WHITE-CELL COUNTS AND PROTEIN LEVELS
			cells/mm ³	g/liter	mmol/liter	cm of water	no./total no. (%)		
First	92	5.2 (2–24)	41.2 (0–842)	0.69 (0.12–2.15)	3.8 (2.0–5.5)	17.4 (3–58)	69/92 (75)	42/69 (61)	27/69 (39)
Second	31	12.1 (4–38)	59.2 (0–720)	0.90 (0.24–5.80)	3.3 (2.0–4.5)	16.1 (8–25)	24/31 (77)	13/24 (54)	11/24 (46)

*Mean values are shown, with the range in parentheses.

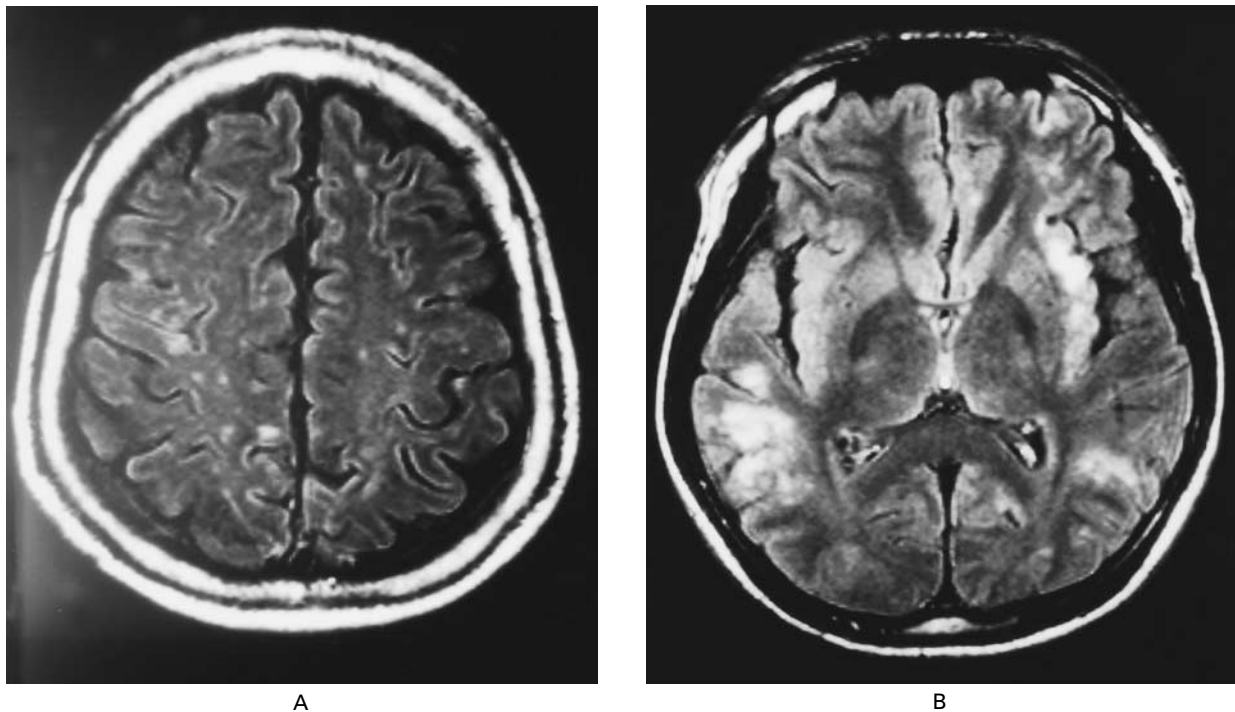


Figure 1. Axial MRI Findings in Patients with Acute (Panel A) and Relapsed (Panel B) Nipah Virus Encephalitis with Use of Fluid-Attenuated Inversion Recovery.

In Panel A, an image of the brain of a patient with acute Nipah virus encephalitis shows multiple discrete hyperintense lesions in the white and gray matter. In Panel B, an image of the brain of a patient with relapsed Nipah virus encephalitis shows confluent lesions involving primarily the cortical gray matter.

levels, or both) in 75 percent and 77 percent, respectively. There was no correlation between abnormal cerebrospinal fluid findings and the severity of disease. The mean Glasgow Coma Scale score at nadir was 11.3 in those with abnormal findings and 9.5 in those with normal findings ($P=0.1$).

The results of computed tomography of the brain, which was carried out in seven patients on admission, were normal. All 27 patients who underwent

MRI of the brain during the acute phase of the illness had widespread focal lesions in the subcortical and deep white matter and, to a lesser extent, in the gray matter on T_2 -weighted sequences and fluid-attenuated inversion recovery sequences (Fig. 1A).

Sixty-three electroencephalograms were obtained in 36 patients. The main abnormalities were diffuse slow waves with focal sharp waves (56 percent); continuous, diffuse, irregular slow waves (31 percent);

and intermittent, diffuse slow waves (11 percent). Focal abnormalities were mainly seen in the temporal regions (75 percent). The electroencephalographic findings were correlated with the severity of the disease. Bilateral temporal periodic complexes of sharp and slow waves every one to two seconds were seen in deeply comatose patients; all such patients died. There was no relation between the electroencephalographic findings and the presence of myoclonus or focal lesions on neuroimaging.

Among the 18 patients from whom cultures were obtained in order to isolate Nipah virus, the virus was isolated from cerebrospinal fluid in 5. Among the 26 patients from whom cultures from other body fluids were obtained, the virus was isolated from tracheal secretions in 5, from urine in 4, and from urine, nasal secretions, and tracheal secretions in 1 (Fig. 2). Tests for antibodies against Hendra virus were performed in 83 patients. Serum samples were positive in 71 percent of patients, cerebrospinal fluid samples were positive in 31 percent of patients, and either or both types of samples were positive in 76 percent of patients. There were no significant differences in demographic and clinical characteristics between patients with antibodies against Hendra virus and the other patients. Among those who were negative for antibodies against Hendra virus or who were not tested, 61 percent had segmental myoclonus. Furthermore, Nipah virus was isolated from two patients who were seronegative and from three patients in whom serologic tests for antibodies against Hendra virus were not performed.

Outcome

Treatment was supportive. Half the patients required mechanical ventilatory support. Seizures were controlled with intravenous phenytoin. Because histopathological studies had shown vasculitis-induced thrombosis,³ aspirin and pentoxifylline were used empirically in 85 percent and 84 percent of patients, respectively. Ribavirin, an antiviral nucleoside analogue, was administered to 78 percent of patients either orally or, in severely ill patients, intravenously.

Thirty patients (32 percent) died, 50 patients (53 percent) recovered fully, and 14 patients (15 percent) had residual neurologic deficits. The mean time from the onset of illness to death was 10.3 days (range, 5 to 29). The direct cause of death in all but two patients was thought to be Nipah encephalitis; one of these two patients died of a massive intracerebral hemorrhage on the 29th day of illness after recovery from coma, and the other died of severe sepsis. All patients with normal levels of consciousness recovered fully after a mean duration of illness of 14.1 days (range, 6 to 24), whereas only eight of the patients (15 percent) with reduced levels of consciousness did so.

Of the 14 patients with residual deficits, 5 remained in a vegetative state. Two patients had residual cognitive impairment and were dependent on caregiv-

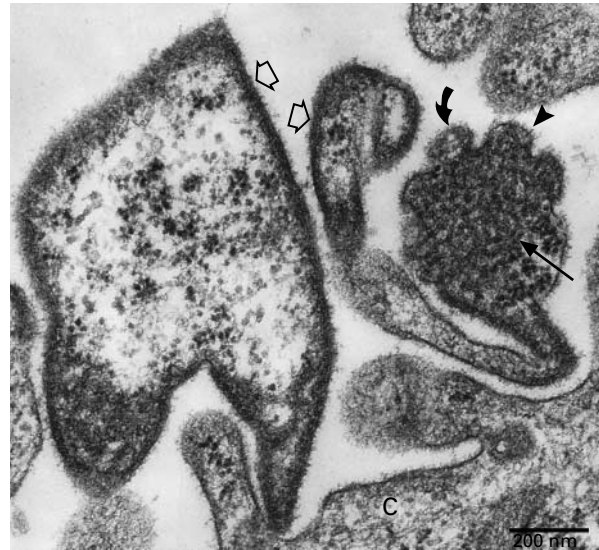


Figure 2. Transmission Electron Micrograph of Nipah Virus.

Pleomorphic viruses in different stages of development can be seen. Developing viruses with putative M protein accumulating beneath the membrane are indicated by the open arrows. A mature virus (curved arrow) contains ribonucleoprotein (thin arrow) and surface projections (arrowhead). The infected Vero cell (C) from which the viruses are forming and budding is at the bottom of the micrograph. (Courtesy of Dr. Alex Hyatt, Commonwealth Scientific Industrial Research Organization, Australia.)

ers. Three patients had mild cognitive disabilities, and two had mild cerebellar disabilities. Two other patients had residual deficits after having a relapse of the disease.

Factors that appeared to affect the survival of patients are summarized in Table 4. As compared with the patients who survived, the patients who died were older and had more severe brain-stem involvement, as evidenced by the presence of a reduced level of consciousness, vomiting, abnormal doll's-eye reflex, abnormal pupils, hypertension, and tachycardia during the course of the illness. Other poor prognostic factors were the presence of segmental myoclonus, seizures, areflexia, more greatly elevated hepatic aminotransferase levels at admission, and lower platelet counts at admission. There appeared to be no significant difference in outcome with ribavirin treatment. Multivariate logistic-regression analysis showed that an abnormal doll's-eye reflex ($P=0.025$) and tachycardia ($P<0.001$) were significantly associated with mortality. The estimated probability of mortality in the presence of both factors was 0.84, whereas it was 0.02 in the absence of both factors.

Relapse

Four patients had late neurologic dysfunction. Three patients had a relapse 13 to 39 days after an initial mild illness. Another patient was seropositive for an-

TABLE 4. FACTORS ASSOCIATED WITH THE PROGNOSIS OF NIPAH VIRUS INFECTION.

FACTOR	DEATH (N=30)	SURVIVAL (N=64)	P VALUE
Mean age — yr	40.9	35.2	0.02
Vomiting — no. (%)	12 (40)	13 (20)	0.04
Mean lowest Glasgow Coma scores	6.8	12.8	0.005
Segmental myoclonus — no. (%)	20 (67)	10 (16)	<0.001
Abnormal doll's-eye reflex — no. (%)	26 (87)	10 (16)	<0.001
Abnormal pupils — no. (%)	29 (97)	20 (31)	<0.001
Hypertension — no. (%)	23 (77)	14 (22)	<0.001
Tachycardia — no. (%)	28 (93)	8 (12)	<0.001
Absent or reduced reflexes — no. (%)	22 (73)	31 (48)	0.02
Seizures — no. (%)	12 (40)	10 (16)	0.01
Mean aspartate aminotransferase level at admission — U/liter	87	34.4	0.001
Mean alanine aminotransferase level at admission — U/liter	94.2	53.6	0.006
Mean platelet count at admission — per mm ³	151,000	197,000	0.005

tibodies against Hendra virus but remained asymptomatic until he became ill 11 weeks later. He subsequently died. One had an isolated nuclear third-nerve palsy, from which she gradually recovered. Three others had altered consciousness, and two of these patients had seizures. Dysphasia and segmental myoclonus with ataxia occurred in one patient each. In three patients, the cerebrospinal fluid examination results were abnormal, with lymphocytic pleocytosis and elevated protein levels; the virus could not be isolated from the cerebrospinal fluid. In patients with relapses or disease of delayed onset, diffuse confluent involvement of the cortical gray matter was found on MRI (Fig. 1B).

Histopathological Findings

Five autopsies were performed. The findings from three patients who died within two weeks after the onset of illness have been described previously.³ These patients had mainly disseminated microinfarctions of the central nervous system as a result of vasculitis-induced thrombosis. The remaining two patients died more than a month after infection. One of these patients had massive intracerebral and intraventricular hemorrhage with severely increased intracranial pressure. Residual parenchymal inflammation and vasculitis were still evident at autopsy. The hemorrhage was attributed to vascular fragility resulting from vasculitis. The other patient had delayed-onset disease with encephalitis but no evidence of vasculitis or microinfarction.

DISCUSSION

The outbreak of Nipah encephalitis was one of the most severe outbreaks of any disease in Malaysia.

Over 200 people were infected, and the outbreak led to the disruption of the pig-farming industry. Most pig farms were small family farms worked by husbands and wives and sometimes their children. The farmers were mainly ethnic Chinese, and the Malay Muslim residents of the villages did not handle pigs. The fact that most patients were Chinese men suggested that the virus was transmitted by direct contact with pigs or their secretions, rather than by mosquitoes, as in the case of Japanese encephalitis.⁸ The unusual sudden death of the pigs suggested that the animals were infected with Nipah virus. The infection seems subsequently to have spread from pigs to humans, possibly by contact with infected secretions.¹ Since some patients had no direct contact with pigs, the virus may be spread by respiratory droplets. Other animals that appear to be susceptible to the disease, such as dogs, seem to be able to transmit the disease to humans as well. The clustering of cases among family members suggested a high attack rate. Human-to-human transmission has not been documented.^{1,2}

Nipah virus appears to have a short incubation period, during which it spreads systematically, as evidenced by isolation of the virus from urine and throat and nasal secretions. The finding of abnormal chest radiographs in several patients indicates possible pulmonary involvement. Our patients had no substantial respiratory symptoms, although pneumonia was reported in three patients with Nipah virus infection from Singapore.⁵ Vasculitis has been identified in the lung and several organs other than the brain in patients with Nipah virus infection,³ and it is possible that vasculitis may become severe enough to cause clinical symptoms.

The mental obtundation and neurologic signs indicate that Nipah virus probably has a predilection for the central nervous system. The disease appeared to be nonencephalitic in only a few patients. Meningism was relatively uncommon, suggesting that primary meningitis was not important. The disease was thought to be due primarily to inflammation of the small blood vessels, with thrombosis and microinfarction, although neuronal invasion also seems to occur.³ The mental changes appeared to be due to diffuse cerebral involvement, which was also indicated by diffuse electroencephalographic and MRI abnormalities. However, the prominent brain-stem dysfunction in comatose patients suggests that specific brain-stem involvement may also be important.

Although some neurologic signs were nonspecific and probably reflected widespread vasculitis, other neurologic features appeared to be characteristic and distinctive, including hypertension, tachycardia, segmental myoclonus, and hypotonia and areflexia. These features suggest a predilection of the virus for certain groups of neurons. Segmental myoclonus indicated focal involvement of neurons in the lower brain

stem, the upper cervical spinal cord, and the lower spinal cord. We are not aware of any other type of encephalitis characterized by similar segmental myoclonus. Tendon areflexia appeared to be primarily central in origin, because of its generalized nature and diffuse occurrence in the presence of relatively normal muscle power and nerve conduction. However, abnormal late responses in nerve-conduction studies in some patients may suggest spinal-root involvement as well. In patients with persistent flaccid tetraplegia, the absence of upper-motor-neuron signs, a positive response to cortical magnetic stimulation, and a subsequent good motor recovery in most patients argue against the presence of a pyramidal lesion. Recovery of cranial motor function in some patients in whom tetraplegia persisted suggests that other descending tracts from the brain stem may be involved.

Tests for antibodies against Hendra virus were not positive in all patients. This may be because the test was directed against antigens of a different, albeit related, virus. Another reason may have been that some patients died before seroconversion. The facts that the clinical characteristics of seropositive and seronegative patients were similar and that Nipah virus was isolated in some seronegative patients indicate that both seropositive and seronegative patients had the same disease. Furthermore, there is no evidence of the presence of a concurrent epidemic of viral encephalitis due to other agents. With the culling of the pigs, the epidemic rapidly died down, confirming that pig-related Nipah encephalitis was the only epidemic.

The results of initial cerebrospinal fluid examination were abnormal in only 75 percent of patients. Although they were important in confirming encephalitis, the abnormalities were nonspecific and were similar to those of other viral encephalitides. MRI of the brain was more sensitive than cerebrospinal fluid examination, and the multifocal lesions (probably corresponding to areas of microinfarction) appeared to be specific for acute Nipah encephalitis. Electroencephalographic changes were also nonspecific. Unlike MRI findings, the degree of electroencephalographic abnormalities (in particular, the presence of periodic complexes) reflected the severity of neurologic involvement and was related to the outcome.

The disease had a high fatality rate. The main cause

of death appeared to be severe neuronal dysfunction, especially in the brain stem. The factors associated with mortality — coma, abnormal doll's-eye reflex, abnormal pupils, hypertension, tachycardia, vomiting, and segmental myoclonus — all indicate severe brainstem involvement. Higher hepatic-enzyme levels and lower platelet counts on admission in patients who died probably reflected nonspecific systemic changes in very ill patients. Very few survivors had severe residual deficits, in contrast to survivors of other encephalitides, such as herpes simplex encephalitis and Japanese encephalitis.

Neurologic relapse may occur after mild or asymptomatic infection. The failure to culture the virus from cerebrospinal fluid and the different histopathological and MRI changes (affecting mainly cortical gray matter) in patients with relapse suggest that the pathophysiologic process differs from that of acute encephalitis. The course and characteristics of the relapse bear some similarities to those in a patient with Hendra virus infection who died of encephalitis 13 months after recovering from his initial illness.⁶ The mechanisms of relapse need to be investigated further.

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