Neurol J Southeast Asia 2001; 6 : 7 – 11

ORIGINAL ARTICLES

Occupational exposure, age, diabetes mellitus and outcome of acute Nipah encephalitis

Heng Thay CHONG, Chong Tan TAN, Khean Jin GOH, Nee Kong CHEW, *Sree Raman KUNJAPAN, *Vijayasingham PETHARUNAM, *Tarmizi THAYAPARAN.

*Division of Neurology, University Malaya Medical Centre, Kuala Lumpur, and *Department of Medicine, Seremban Hospital, Negeri Sembilan, Malaysia.*

Abstract

The outbreak of acute Nipah encephalitis in Malaysia in 1998 and 1999 affected 256 patients with 105 mortalities, as well as decimated the local pig farm industry. The outbreak from the novel Nipah virus was attributed to close contact with infected pigs. In the pathogenesis of the disease, the level of exposure to sick animals and host factors were not known. We undertook a retrospective study of 194 patients from the University Malaya Medical Centre and Seremban Hospital to examine these. The level of exposure to sick animals had no effect on the outcome of human disease. The diabetic patients had similar clinical presentations and laboratory findings as non-diabetic patients, apart from higher serum and cerebrospinal fluid sugar levels, with more patients having renal impairment, and more severe autonomic dysfunction with higher blood pressure and temperature. On Cox regression analysis, the diabetic patients had increased mortality by 123% ($p<0.001$). We concluded that outcome of acute Nipah encephalitis was not related to the level of exposure to the sick animals, but was related to concomitant diabetes mellitus, probably due to immunoparesis.

INTRODUCTION

From September 1998 to May 1999, an outbreak of Nipah encephalitis occurred in Malaysia involving the workers associated with pig farm industry. There were 256 patients, 105 of whom were fatal.[1-4] The causative agent, the Nipah virus, was a novel Paramyxovirus related to the Hendra virus.[3,5,6] Previous studies[7,8] have suggested that death was probably due to severe brain-stem involvement.[7,8] Epidemiology studies suggested that close contact with sick animals was strongly associated with infection. Different activities within the pig industry expose the workers to different degrees of risk to developing Nipah virus infection.[4,9,10] As for outcome of the disease, earlier studies suggested that older age may be associated with increased mortality.[8,11] To date there is no study that show if the level of exposure to the virus or other host factors are important in determining the severity and outcome of the disease. Diabetes mellitus is a well-known cause of vasculopathy and immunoparesis.[12,13] We retrospectively study a larger group of patients to determine the correlation between occupation, age, diabetes mellitus and outcome of acute Nipah encephalitis.

METHODS

The medical records of the Nipah encephalitis patients who were admitted to the University Malaya Medical Centre and Seremban Hospital were examined retrospectively. The two Hospitals were the epicenters treating more than four fifth of the patients during the outbreak. Patients were considered to have Nipah encephalitis if they came from the areas known to be involved in the outbreak, had direct contact with pigs or other infected animals, and had evidence of encephalitis. Encephalitis was defined by the presence of one of the followings: clinical features (fever, headache, altered sensorium, or focal neurologic signs), abnormal cerebrospinal fluid findings ($\geq$ 6 lymphocytes per cubic millimeter, or a protein level of $\geq$ 0.45 g/l in patients who were under 50 years of age and $\geq$ 0.50 g/l in patients older than 50 years of age) or characteristic findings in the magnetic resonance imaging of the brain.[7,8,14] The pig farm owners and workers were classified as having high exposure, while those who had infrequent contacts with pigs were considered to have low exposure. The primary outcome measure was mortality, and secondary measures

Address correspondence to: Dr HT Chong, Neurology Laboratory, University Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia

were the need for mechanical ventilatory support, length of hospital stay, residual neurological deficits, and development of relapse encephalitis. We also compared various clinical and laboratory parameters between the diabetic and non-diabetic patients.

For statistical analysis, univariate parametric variables were analyzed with ANOVA, nominal non-parametric variables were analyzed with χ^2 or Fisher exact test, and ordinal non-parametric variables with Mann-Whitney rank-sum test. For multivariate survival analysis we used Cox regression model.

RESULTS

One hundred and ninety-four patients who satisfied the definition of acute Nipah encephalitis were analysed. The means age was 38 $\pm$ 13 years, with 165 (85%) males and 29 (15%) females. There were 135 (70%) Chinese, 38 (20%) Indians, 16 (8%) migrant workers mainly from Bangladesh and Nepal, 4 (2%) East Malaysians and one (0.5%) Malay. One hundred and fifty-five patients (80%) had high exposure to sick animals, with 95 (49%) pig farm owners, and 60 (31%) workers. Thirty-nine patients (20%) had low exposure to sick animals comprising of 8 (4%) transportation workers, 3 (1.5%) cullers, 2 (1%) abattoir workers and 26 (13%) other workers who infrequently came into contact with sick animals. Of the 26 "other workers", apart from one patient who worked as a clerk in a pig farm, the other 25 patients were engaged in occupations not directly related to pig farming. There were 10 (5%) patients who had past history of diabetes mellitus.

The characteristics of the patients with high exposure and low exposure to sick animals and their outcome were compared in Tables 1 and 2. As shown, there was no significant difference in the characteristics and outcome of the two groups of patients.

The demographic characteristics, clinical features and laboratory findings of the diabetes and non-diabetic patients is shown in Tables 3-5. For patients who moved out from the outbreak area, the incubation period was calculated as the

TABLE 1. The characteristics of patients with high and low exposure to sick animals

Parameters	High exposure (n=155)	Low exposure (n=39)	P values
Means age ± SD / years	39 ± 12	35 ± 13	0.078
Male : Female ratio	131:24	34:5	0.87
Proportion of Chinese	74%(n=114)	54%(n=21)	0.028
Admission systolic blood pressure in mmHg	132 ± 20	133 ± 17	0.85
Admission diastolic blood pressure in mmHg	80 ± 14	79 ± 13	0.65
Admission heart rate/bpm	86 ± 17	87 ± 16	0.76
Admission temperature/°C	38.1 ± 0.9	37.9 ± 0.9	0.24
Admission GCS* Score (median)	15	15	0.40
Proportion treated with ribavirin	70%(n=109)	80(n=31)	0.35
Proportion with diabetes mellitus	6%(n=9)	3%(n=1)	0.69

*GCS – Glasgow Coma Scale, full score of 15

TABLE 2. Outcome measures in patients with high and low exposure to sick animals

Parameters	High exposure (n=155)	Low exposure (n=39)	P values
Mortality	40%(n=62)	31%(n=12)	0.38
Proportion ventilated	58%(n=90)	49%(n=19)	0.36
Hospital stay in days (median)	10.0	9.0	0.19
Residual neurological deficits	23%(n=18/79)*	9%(n=2/22)*	0.25
Relapse Nipah encephalitis	5%(n=8)	0%(n=0)	0.32

*The denominator are the number of survivors only.

interval between the last day of exposure and the onset of symptoms. The diabetic patients were older (Table 3). The diabetic patients did not differ from the non-diabetic in their incubation period and clinical symptoms. However, the diabetic patients had higher admission blood pressures and peak blood pressures as well as peak temperature (Table 4). They also had higher peak serum sugar, cerebrospinal fluid sugar and peak serum creatinine levels (Tables 5). On logistic regression analysis however, the only statistical significant difference between the diabetic and the non-diabetic patients was that the former had higher peak diastolic blood pressure (p=0.015).

The outcome measures of the diabetic and non-diabetic patients is shown in Table 6. As shown, the diabetic patients had a higher mortality of 80%, as compared with 36% among the non-diabetic patients. This translates to a relative risk of 2.4 (95% CI 1.6 -3.6) or a 123% increase in mortality. Diabetes mellitus, however,

TABLE 3. Demographic characteristics of diabetic versus non-diabetic patients

Parameters	Diabetes mellitus (n=10)	Non-diabetes mellitus (n=184)	P values
Means age ± SD in years	51 ± 4	37 ± 12	<0.001
Proportion of male	90%(n=9)	85%(n=156)	>0.9
Proportion of Chinese	90%(n=9)	65%(n=126)	0.29
Proportion of patients with high exposure to sick animals	90%(n=9)	79%(n=146)	0.69
Proportion treated with ribavirin	60%(n=6)	73%(n=134)	0.47

TABLE 4. Clinical features of the diabetic and non-diabetic patients

Parameters	Diabetes mellitus (n=10)	Non-diabetes mellitus (n=184)	P values
Incubation period in days	5.0 ± 0.0 (n=4)	9.4 ± 8.8 (n=123)	0.32
Fever	100%(n=10)	98%(n=175)	1.0
Headache	90%(n=9)	77%(n=142)	0.46
Dizziness	40%(n=4)	36%(n=67)	0.5
Cough	30%(n=3)	21%(n=39)	0.45
Myalgia	50%(n=5)	29%(n=53)	0.17
Vomiting	30%(n=3)	32%(n=58)	1.0
Seizures	20%(n=2)	27%(n=49)	1.0
Admission systolic blood pressure in mmHg	152 ± 33	131 ± 18	<0.001
Admission diastolic blood pressure in mmHg	89 ± 18	80 ± 14	0.039
Admission heart rate per minute	90 ± 17	86 ± 17	0.41
Admission temperature in °C	38.2 ± 0.7	38.0 ± 0.9	0.57
GCS* on admission (median)	15	15	0.39
GCS* at nadir (median)	12	9	0.84
Brainstem signs	70%(n=7)	58%(n=106)	0.53
Peak temperature in °C	40.4 ± 0.8	39.3 ± 1.2	<0.001
Peak heart rate per minute	134 ± 18	119 ± 30	0.12
Peak systolic blood pressure in mmHg	209 ± 34	164 ± 32	<0.001
Peak diastolic blood pressure in mmHg	120 ± 26	94 ± 17	<0.001

*GCS – Glasgow Coma Scale score, maximal of 15.

has no effect on the need of mechanical ventilation, the length of hospital stay, the proportion with residual neurological deficits, as well as relapse encephalitis. There was also no difference between the diabetic and the non-diabetic in terms of complications. The non-diabetics were just as likely to get pneumonia (21% versus 29%, p=0.64), septicaemia (14% versus 10%, p=1.0), bedsores (11% versus 0%, p=1.0) and arrhythmia (8% versus 0%, p=1.0). Patients with older age, higher systolic and diastolic blood pressures and lower Glasgow Coma Scale score on admission were also found to have higher mortality (p<0.001, p=0.0015, p=0.018 and p=0.024 respectively) and were more likely to be ventilated (p=0.002, p<0.001, p<0.001 and p<0.001 respectively). On Cox regression analysis, a past history of diabetes mellitus, together with the use of Ribavirin and systolic hypertension on admission were found to be statistically significant prognostic factors for mortality (p<0.001, p<0.001 and p=0.011 respectively). Older age, defined as ≥ 40 years, was however, not statistically significant (p=0.09)

DISCUSSION

Although degree of exposure to sick animals has been shown to influence the risk of developing Nipah virus infection[4,9,10], this study has shown that once infected, the level of exposure to sick animals do not affect the severity and outcome of the disease. This is consistent with the study on asymptomatic Nipah virus infection, where the degree of exposure to sick animals did not affect the likelihood of cerebral involvement in infected patients as shown by the abnormal brain magnetic resonance imaging.[15]

As for the host factors in determining the outcome fo the infection, this study showed the importance of diabetes mellitus. In this study, the diabetic patients had the same initial clinical presentation as the non-diabetic patients. However, they had more severe disease manifestations with more prominent autonomic disturbances, as seen in higher blood pressure, heart rate and temperature. On laboratory testing, they also had higher peak serum sugar, cerebrospinal fluid sugar and were more likely

TABLE 5. Laboratory findings in the diabetic and non-diabetic patients

Parameters	Diabetes mellitus (n=10)	Non-diabetes mellitus (n=184)	P values
Trough platelets count in 10^9/μl	137 ± 82	162 ± 72	0.29
Peak serum sugar in mmol/l	18.1 ± 6.3	11.1 ± 5.1	0.0015
Peak creatinine in μmol/l	264 ± 231	134 ± 123	0.017
Proportion with abnormal CSF*	38%(n=3)	61%(n=106)	0.27
CSF protein in g/l	0.55 ± 0.16	1.2 ± 3.2	0.15
CSF sugar in mmol/l	5.9 ± 1.6	4.3 ± 3.0	0.0017
CSF cell count / ml	6 ± 9	52 ± 135	0.73
Aspartate transaminase in IU/l	73 ± 53	78 ± 91	0.74
Alanine transaminase in IU/l	97 ± 63	92 ± 95	0.52
Proportion with positive Hendra serology	80%(n=8)	72%(n=131)	0.73

*CSF – Cerebrospinal fluid, available in 8 of the diabetic patients, and 173 in the non-diabetic patients. Abnormal CSF is as defined in text.

TABLE 6. Outcome measures in the diabetic and non-diabetic patients

Parameters	Diabetes mellitus (n=10)	Non-diabetes mellitus (n=184)	P values
Mortality	80%(n=8)	36%(n=66)	0.38
Proportion ventilated	80%(n=8)	55%(n=101)	0.19
Hospital stay in day (median)	38.4 ± 95.8	18.8 ± 33.5	0.17
Residual neurological deficits	0%(n=0)	20.4%(n=20)	0.60
Relapse Nipah encephalitis	10%(n=1)	4%(n=7)	0.35

to develop renal impairment. On Cox regression analyses, the patients with diabetes mellitus had increased mortality by up to 123%. This difference was not accounted for by the older mean age among the diabetic patients and was independent of the use of ribavirin.

Diabetes mellitus causes a wide range of complication, including metabolic disturbances, micro- and macrovasculopathies and neuropathy. Diabetes mellitus also causes a wide range of disturbances in the immune system, involving both the humoral and cellular mediated responses. On the humoral arm, diabetic patients have lower complement factor IV, and decreased cytokine response on stimulation. On the cellular arm, the polymorphonuclear cells, monocytes and macrophages in diabetic patients have poorer chemotaxis, phagocytosis and cell killing abilities.[12,13] It is likely that the impaired immune responses are responsible for the worse outcome in diabetic patients with acute Nipah encephalitis.

Although earlier studies has suggested the importance of older age[8,11], this was not substantiated in this study with larger number of patients, and with multivariate analysis. The diabetic patients who were generally older probably accounted for the older age as a prognostic factor in the earlier analysis. The beneficial effect of ribavarin in reducing mortality is being discussed in a separate paper.[16]

REFERENCES

1. CDC. Outbreak of Hendra-like virus: Malaysia and Singapore, 1998-1999. MMWR Morb Mortal Wkly Rep 1999;48:165-9.
2. CDC Update. Outbreak of Nipah virus: Malaysia and Singapore, 1998-1999. MMWR Morb Mortal Wkly Rep 1999;48:335-7.
3. Chua KB, Bellini WJ, Rota PA *et al.* Nipah virus: A recent emergent deadly Paramyxovirus. Science 2000;288:1432-5.
4. Parashar UD, Lye MS, Ong F. *et al.* Case Control Study of Risk Factors for Human Infection with a New Zoonotic Paramyxovirus, Nipah Virus, during a 1998-1999 Outbreak of Severe Encephalitis in Malaysia. The Journal of Infectious Diseases. 2000;181:1755-9.
5. Chua KB, Goh KJ, Wong KT *et al.* Fatal encephalitis due to the Nipah virus among pig-farmers in Malaysia. Lancet 1999;354:1257-1259.
6. Harcourt B, Tamin A, Ksiazek TG *et al.* Molecular characterization of Nipah virus, a new emergent paramyxovirus. Virology 2000;271:334-9.
7. Goh KJ, Tan CT, Chew NK *et al.* Clinical Features of Nipah Virus Encephalitis Among Pig Farmers in Malaysia. N Eng J Med 2000;342:1229-35.
8. Chong HT, Kunjapan SR, Thayaparan T *et al.* Nipah Encephalitis Outbreak in Malaysia; Clinical Features in patients from Seremban. Neurol J Southeast Asia 2000;5:61-8.
9. Chew MHL, Arguin PM, Shay DK, Goh KT, Rollin PE, Shieh WJ, Zaki SR, Rota PA, Ling AE, Ksiazek TG, Chew SK and Anderson LJ. Risk factors for Nipah virus infection among abattoir workers in Singapore. J Inf Dis 2000;181:1760-3.
10. Tan KS, Tan CT, Goh KJ. Epidemiology aspects of Nipah virus infection. Neurol J Southeast Asia 1999;4:77-81.
11. Chua KB, KB, Lam SK, Tan CT *et al.* High mortality in Nipah encephalitis is associated with presence of virus in cerebrospinal fluid. Ann Neurol 2000;48:802-5.
12. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26:259-65.
13. Fontana G, Lapolla A, Sanzari M, Piva E, Mussap M, De Toni S, Plebani M, Fusetti F, Fedele D. An immunological evaluation of type II diabetic patients with periodontal disease. J Diabetes Complications 1999;13:23-30.
14. Ahmad Sarji S, Abdullah BJ, Goh KJ, Tan CT, Wong KT. MR Imaging features of Nipah encephalitis. AJR 2000;175:437-2.
15. Tan KS, Ahmad Sarji S, Tan CT, Abdullah BJJ, Chong HT, Thayaparan T, Koh CN. Patients with asymptomatic Nipah virus infection may have abnormal cerebral MR imaging. Neurol J Southeast Asia 2000;5:69-73.
16. Chong HT, Kamarulzaman A, Tan CT, Goh KJ, Thayaparan T, Kunjapan SR, Chew NK, Chua KB, Lam SK. Treatment of acute Nipah encephalitis with ribavarin. Ann Neurol 2001;49:810-3.