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Epidemiological aspects of Nipah virus infection

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Abstract

An outbreak of Nipah encephalitis secondary to a new paramyxovirus virus occured among pig farmers in Malaysia from September 1998 to June 1999. The objective of this study was to characterize several epidemiological aspects of the outbreak. The study was based on patients admitted to the University Hospital, Kuala Lumpur and their household members. Fourteen households with 110 members were studied. Thirty out of 110 (27%) of the household members had symptomatic Nipah infection. Another 6 out of 43 (8%) members had subclinical infection with positive serology with a total of 33% of the household members being infected by Nipah virus. There was significant correlation between full time pig farming and the likelihood of Nipah infection. Twenty-five out of 43 members (51%) who had high exposure to pigs had symptomatic Nipah infection whereas 5 out of 24 members (21%) who had minimum exposure to pigs were infected. Half of the 14 households reported sick or dying pigs. There was no correlation between the rate of symptomatic human Nipah infection and history of animals falling sick (p=0.8). The cases indicated that the infection may spread from pig to man via infected body fluid with direct body contact and via respiratory droplets at close range. Animals other than pigs may also transmit the disease to man and from pig-to-pig.

Key words: Nipah virus, encephalitis, epidemiology, Malaysia

INTRODUCTION

From September 1998 to June 1999, there was an outbreak of viral encephalitis in several pig farming villages in Malaysia.[1] The outbreak subsequently spread to involve abbatoir workers in Singapore.[2] More than 200 patients were affected nationwide and close to 100 patients were admitted to the University Hosptial, Kuala Lumpur.[3] The cause of the outbreak was identified to be a new paramyxovirus closely related to Hendra virus, later named Nipah virus as the first isolate was from a patient from Sungei Nipah Village.[4,5] The clinical, pathological, radiological and EEG features of the Nipah encephalitis have been described.[2-7] This is a study to characterize some of the epidemiological aspects of the disease. In particular, the aims of this study was to determine the relationship of the disease to pig farming, the possible modes of transmission, the Nipah virus infection rate and the rate of asymptomatic infection.

MATERIALS AND METHODS

The index patients were pig farmers from the patient cohort admitted to the University Hospital, Kuala Lumpur with confirmed Nipah infection. Other patients from the same household were also included with the index case while the household members were recalled and studied. Interviews were conducted using a standardized questionnaire. The information pertaining to any clinical symptoms, the farming activities and conditions of the pigs were obtained. Hendra serology was performed on the household members. The interviews were conducted by the investigator (KST). The study subjects were classified as having *high* exposure if pig farming was their full-time activity. They were defined as having *minimum* exposure if they had occasional, or no activities related to pig farming. Illustrative cases of Nipah infection indicative of the mode of infection from the patient cohort admitted to the University Hospital Kuala Lumpur were reported.

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

Descriptive and comparative statistical data were analysed with a standard statistical software package. Means, standard deviations, medians and ranges were presented for continous

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variables. Chi-square analyses were performed where appropriate for differences between the two groups, related to the degree of pig farming exposure. P values < 0.05 were considered as significant.

RESULTS

Fourteen households were included in the study with a total of 110 subjects. Thirty seven members of the households declined the interview and Hendra serology examination. However, their clinical history were available from the other household members and they were all clinically asymptomatic.

The mean age of the 73 household members who consented to the interview and serology was 34.7 years (14 to 64 years). The male to female sex ratio was 2.5 : 1. The ethnic composition was: Chinese (81%) and Indians (19%). Of the 110 household members, there were 30 members (27%) with symptomatic Nipah infection. Of the 43 clinically well members who were subjected to serology examination, 6 (8%) were found to be positive indicating a previous subclinical infection. Thus, overall 35% of the household members had Nipah infection, the majority were symptomatic.

Of the 73 household members, 49 members had high exposure and 24 had minimum exposure as defined above. Of those with high exposure, 25 (51.0%) had symptomatic Nipah infection. Of those with minimum exposure, 5 (20.8%) had symptomatic infection. There was statistically significant difference ($p<0.03$) in the association of high exposure and symptomatic Nipah infection. The odds ratio was 4 (95% confidence interval; 1.14 - 14.5) while the relative risk was 1.5 (95% confidence interval 1.1– 2.0).

The average number of family members in each household was 7.9. Seven out of 14 households (50%) reported their pigs to have unusual sickness prior to and during the outbreak. There was no statistically difference between the number of ill patients from the households with symptomatic pigs as compared to the households which reported no evidence of sick pigs ($p= 0.8$).

Illustrative case reports

Case one was a pig cagerepairman who denied entering or being in the proximity of the pig farms prior to the illness. He presented with fever and altered sensorium. There was abnormal cerebrospinal fluid and positive serology. He subsequently deteriorated and had to be ventilated. He eventually recovered with no residual neurological signs.

Case two was a 51 year old Muslim army major who supervised the pig culling operation. Being a Muslim where pigs are considered unclean, he was in close proximity with the pigs but denied any body contact. He became ill three days after the culling operation. There was positive serology with abnormal CSF. The patient had uneventful recovery with no residual signs .

Case three was a 57 year old cabinet and wooden box maker. His residence was near to the pig farms but the patient did not enter the farm nor was he in close proximity to the pigs. The patient had two pet dogs which became ill and he had personally nursed them. The dogs subsequently died just before patient became ill. He presented with fever, headache and drowsiness and became deeply comatose with associated myoclonus. There was positive serology with abnormal CSF. The patient remained in vegetative state after the acute febrile illness.

Case four was a 26 year old pig farmer who reported that some of his pigs had unusual sickness and was involved in the culling of pigs in his own farms. He had fever, headache and altered sensorium clinically but recovered without any residual neurological deficits. His CSF was abnormal and the Hendra serology was positive. The patient's pigs were indigenous to the farm, and he denied importing pigs from other neighbouring farms or outbreak areas in other states. The next pig farm was some 100 yards away and the patient denied entering the neighbour's farms.

DISCUSSION

The outbreak of Nipah encephalitis initially involved pig farming villages in Ulu Piah, Tambun and Ampang around Ipoh which is about 200 km north of Kuala Lumpur. The outbreak subsequently involved the pig farming villages in Sikamat, Bukit Pelanduk (including Sungei Nipah and Kampong Sawah, Figure 1), Tanah Merah in the State of Negri Sembilan south of Kuala Lumpur, as well as Sepang and Sungei Buloh in Selangor. Most of the patients were from Bukit Pelanduk. The cluster of pig farm villages in Bukit Pelanduk has a population of about ten thousand. Most of the population were ethnic Chinese, the rest were Indians and

Malays. The main economic activity of the village was pig farming and its related supporting services. With its neighbouring area, it has a pig population of more than one million before the outbreak. The number of pigs in each farm range from 50-20000. Most of these pig farms were small holdings with 2000 pigs or less. The respective family members worked on these farms with the adult male family members working on the farm full time, whereas the adult females and the children helped in the farm part-time. There were also hired workers, many of whom were foreigners from Nepal, Myanmar and Indonesia.

This study showed that Nipah virus caused a disease with high infection rate, affecting 33% of the household members of infected farms, 27% being symptomatic. The rate of symptomatic infection for those who worked as farmers full time was higher at 51%. This is consistent with a high rate of 56% of family members affected by the infection in the cohort of patients admitted to hospital.[3] The infection caused subclinical disease in 8% of the household members in the infected farms. Parashar et al, in a case control study, estimated the asymptomatic seropostive rate to be 11%.[8] In Singapore, there were two who had asymptomatic positive Nipah serology positives versus 11 with clinical disease among the abattoir workers.[9] The higher rate of symptomatic infection versus subclinical disease is in contrast to Japanese encephalitis, where only one out of 300 infected subjects had symptomatic encephalitis.[10] Japanese encephalitis, another encephalitis related to pig farming, was the main differential diagnosis in the initial outbreak.

This study demonstrated the correlation between full time farming with high exposure to pigs and the development of Nipah infection. It is consistent with the hypothesis that the virus was transmitted by direct or close contact with pigs. This is also consistent with the demographic characteristics of the infection, which mainly

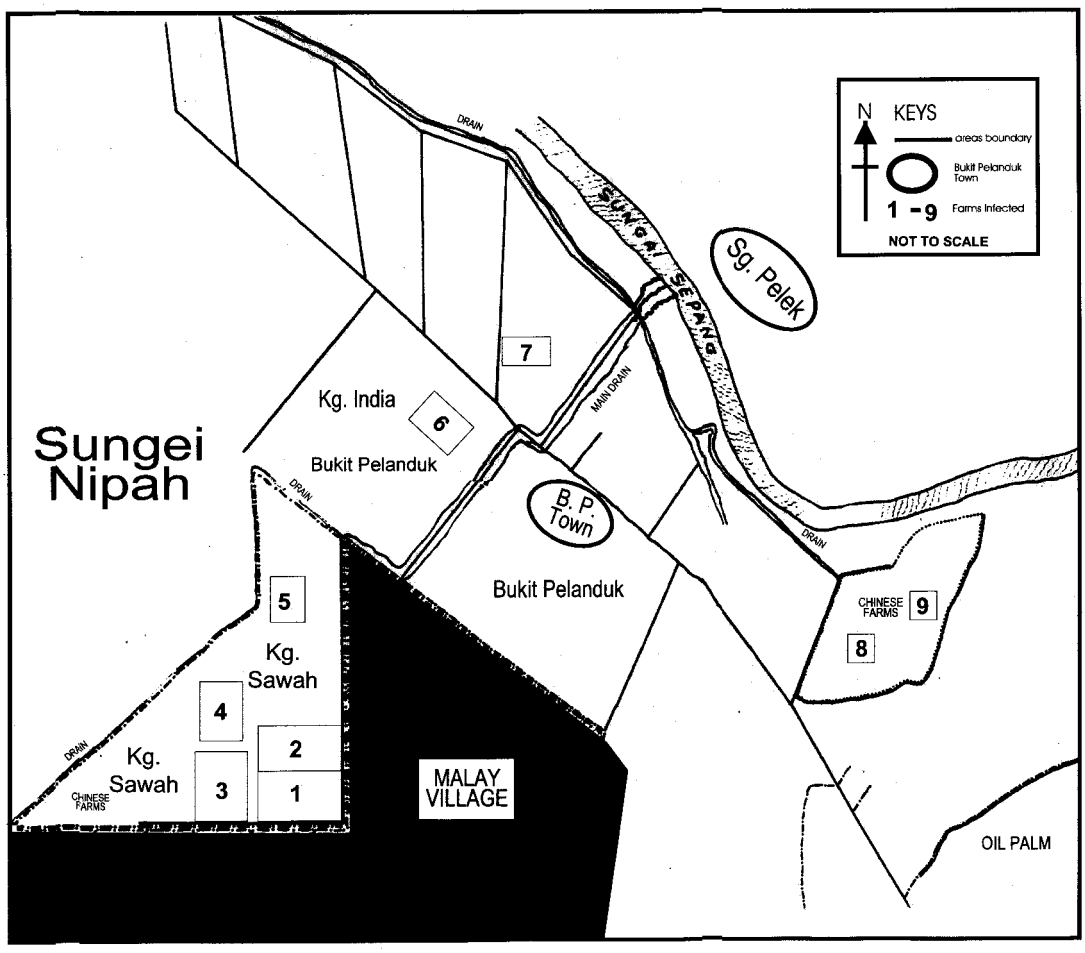

Fig. 1: Map of pig farming villages in Bukit Pelanduk

affected the adult Chinese male of the respective households.[3] Parashar et al reported that there was significant association between Nipah infection and performing activities involving close contact with pigs, such as processing baby pigs (clipping tails, tagging ears), injecting or medicating pigs, assisting in pig breeding (collection of semen from boars, artificial insemination of sows), assisting in the birth of piglets and handling dead pigs. On the other hand, infection was not associated with performing activities that usually did not involve contact with pigs, such as cleaning pigpens and washing pigs with a hose.[8] Contact with live pigs was also found to be the important risk factor for Nipah infection among abattoir workers in Singapore.[9] Figure 1 is a map showing the geographical location of the affected pig farms. As shown, the patients were from the affected farms which were in close proximity with the Malay villages. However, there was no patient reported from the Malay villages. The residents of the Malay villages were Muslims who for religious reason would shun any physical contact with pigs. There was no Nipah encephalitis patient reported from the Malay villages. The evidence that close proximity to infected pigs is necessary for transmission of Nipah infection is also seen in the absence of reported cases of Nipah infection from pig farms in Sungei Pelek across the Sepang River, north of Bukit Pelanduk (Figure 1). Case one and two illustrated that infected secretions through body contact and respiratory droplets at close range may cause the spread of the infection from pig to man.

Fifty percent of households in this study and 41% of the cohort of Nipah virus infection patients admitted to the hospital[3] reported that there was unusual sickness and death of their animals. However , this study showed that there was no statistical significance in the association between the sick animals and development of human disease. This suggest that asymptomatic animals were able to transmit the Nipah virus. This is consistent with the report of Nipah virus infection from the abattoir workers in Singapore, where there was also no unusual sickness detected in the pigs.[2] On the other hand, there was an association between reports of sick and dying pigs and patients in a case control study by Parashar et al.[8] Extensive involvement of the respiratory tract with positive immunohistochemistry to Nipah virus antigen has been shown in the pigs. The antigens were also seen in the pig's kidney and brain.[5] Observations in animals reported that most infected pigs were asymptomatic or manifested only subtle evidence of illness. Some were symptomatic depending on its age. These included fever, laboured breathing, loud cough, trembling, muscle spasms, unco-ordinated gait, agitation, seizure, inability of swallow and frothy salivation.[11]

Case three demonstrated that although pigs were the predominant agent of transmission of Nipah virus from pig to man, infected dogs may also transmit the disease to man. Case four showed that other intermediary animals may be involved with transmission of disease from one pig farm to another.

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