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Patients with asymptomatic Nipah virus infection may have abnormal cerebral MR imaging

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Abstract

Background: An outbreak of severe encephalitis occurred in Malaysia among the pig farmers from September 1998 to April 1999. It was due to a newly discovered paramyxovirus, Nipah virus. Epidemiological studies have showed that up to 11% of the household members of the infected farms had asymptomatic infection. *Objectives:* To determine the presence of cerebral MR imaging abnormalities in subjects with asymptomatic Nipah virus infection and to correlate the MR imaging abnormalities with degree of exposure to sick animals. *Methods:* MR imaging of the brain with spin-echo T1- and T2-weighted sequences and T2-weighted fluid attenuated inversion recovery (FLAIR) sequences were performed on the subjects with asymptomatic infection. *Results:* Thirty-two subjects were studied. MR imaging abnormalities were detected in 5 subjects (16%), one of whom was a nurse who worked with the patients with acute Nipah encephalitis during the outbreak and was not exposed to sick animals. The abnormalities consisted of multiple, discrete, small high signal lesions seen in the subcortical and deep white matter of the cerebral hemispheres, best seen on the FLAIR images. There was no correlation in the degree of exposure to sick animals between the 5 subjects with abnormal brain imaging and 10 age and sex matched controls with positive anti-Nipah antibody and normal cerebral MR imaging. No progression of the lesions was seen in the follow-up scan in one subject. The subjects remained well 20 months after the initial outbreak.
C*onclusion*: Abnormal cerebral MR imaging was seen in 16% of subjects with asymptomatic Nipah virus infection. One of the subjects with abnormal cerebral MR imaging was a nurse, indicating that the infection could be spread from human-to-human.

Key words: Nipah virus infection, asymptomatic, MRI

INTRODUCTION

An outbreak of encephalitis affecting pig farmers and their families occurred in Malaysia from September 1998 to April 1999. The etiology was subsequently found to be a novel paramyxovirus closely related to Hendra virus, later named Nipah virus, as the first isolate was from a patient from Sungei Nipah village.[1,2]

The newly discovered Nipah virus caused an acute febrile encephalitic illness in humans with high mortality. The clinical, epidemiology, pathology, radiology, EEG and serology features have been previously described [3-14] with the illness presenting as fever, headache, dizziness and vomiting. The mortality was high and severe cases who subsequently died were characterized by rapid neurological deterioration culminating in coma, segmental myoclonus and death.

Other than *acute Nipah encephalitis* as described above, Nipah virus also caused *non-encephalitic Nipah infection*[3], defined as systemic illness without encephalitis; *late-onset encephalitis*[3,8], where there is a long latency between the exposure to the sick animals and encephalitis; *relapse Nipah encephalitis*[3,8], where there is recurrent neurological disease after recovery from an initial acute encephalitis, and *asymptomatic Nipah virus infection*[7] where there is development of anti-Nipah antibody without clinical symptoms. Previous studies have shown that asymptomatic Nipah infection was seen in 8-11% of the inhabitants of the infected pig farms.[5-7]

The MR imaging studies has shown that it is a sensitive and specific diagnostic tool in acute Nipah encephalitis.[8] The characteristic changes were small, discrete lesions measuring 2 to 7 mm, disseminated in the subcortical and deep white matter of the cerebral hemisphere, best seen in T2-weighted fluid attenuated inversion recovery (FLAIR) sequences. The number of lesions varies from two to innumerable. Lesions were also seen in the cerebral cortex. There was a lack of edema and mass effect around the

lesions. There was no correlation between the findings on MR imaging and focal neurological signs. The lesions were thought to represent the main pathological finding of widespread vasculitis-induced thrombosis and microinfarcts found at autopsy of fatal cases.

This is a study of MR imaging in patients with asymptomatic Nipah virus infection. The aims were to determine the presence and the extent of subclinical cerebral involvement in the asymptomatic subjects and whether the MR imaging abnormalities were related to the degree of virus exposure.

METHODS

The study subjects consisted of patients with asymptomatic Nipah virus infection. They were recruited from the various epidemiology studies conducted by the University Malaya Medical Centre, Ministry of Health, Malaysia and the Centre for Disease Control, Atlanta, U.S. during the outbreak.[5,7] The studies involved the hospital staffs, farm workers, veterinary workers, army personnel, abattoir workers and butchers who in one way or the other, were exposed to the sick animals or were involved with the care of the patients with acute Nipah encephalitis. A total of 59 subjects were found to have asymptomatic Nipah virus infection with positive anti-Nipah antibody but no clinical evidence of infection. These patients have been followed up regularly in the various clinics and hospitals near their residence in Port Dickson, Seremban and Kuala Lumpur. They were requested to undergo further evaluation and MR imaging at the University Malaya Medical Centre, Kuala Lumpur.

Information obtained from the study subjects included the demographic data, clinical symptoms, and specific pig farming activities whereby the subjects were classified into high exposure or low exposure to sick animals. The degree of exposure to the sick animals was compared between those with brain MR imaging abnormalities and 10 age and sex matched control subjects with normal cerebral MR imaging. The control subjects were also positive for anti-Nipah antibody.

For serology, the sera were tested with an IgM-capture enzyme linked immunosorbent assay (ELISA) and indirect IgG ELISA antibodies against Hendra virus antigen.

MR imaging was performed using a 1.5 Tesla superconducting system (Vision; Sieman, Erlangen, Germany). The MR imaging sequences were spin-echo T1- (TR/TE, 650/14; one excitation), spin-echo T2- (3800/90; two excitations) and T2-weighted fluid inversion recovery sequence (FLAIR) (9000/110; one excitation). Inversion time was 2500 msec. Images were obtained in the axial plane with a 10 mm slice thickness. Two radiologists evaluated the MR images.

For statistical analysis, descriptive and comparative statistics were performed using a standard statistical software package. Chi square analyses were used where necessary.

RESULTS

A total of 59 subjects with asymptomatic Nipah virus infection were identified but only 32 consented to the study. The mean age was 33 years (range: 12-58 years). Twenty-two subjects were male (69%) and 10 (31%) were females. The largest group consisted of 22 subjects (69%) who were pig farmers and their household members. Eight subjects (25%) were veterinary personnel and two (6%) were nurses.

The brain MR imaging was performed up to 18 months following the serology status was known. Abnormal MR imaging was seen in 5 subjects (16%). The abnormalities were similar to that seen in acute Nipah encephalitis.[8] It consisted of the presence of multiple, small discrete high-signal-intensity lesions, best seen on FLAIR sequence. They were found mainly in the subcortical and deep white matter of the cerebral hemispheres. Neither mass effect nor edema was seen. The number of lesions was less than that seen in the acute Nipah encephalitis with only one subject showing more than 20 lesions (Table 1). In one subject with abnormal MR imaging, the repeat scan three months later showed no significant change.

The demographic and features and MR imaging changes of the 5 subjects with abnormal brain MR imaging is listed in Table 1. One of the subjects with abnormal MR imaging was a 39-year-old nurse who worked in the Intensive Care Unit where the acute Nipah encephalitis patients were managed during the outbreak (Figure 1). Another subject was a 52-year-old veterinary assistant involved in the culling operations. Three other subjects were pig farmers, all had household members with acute Nipah encephalitis. All the 5 subjects were otherwise healthy, with no evidence of diabetes or hypertension.

There was no statistically significant difference in the degree of exposure to sick animals between the 5 subjects with abnormal

Table 1. Demographic features and imaging changes of subjects with asymptomatic Nipah virus infection and abnormal cerebral MR imaging.

	1	2	3	4	5
Age in years	52	41	52	46	49
Sex	Male	Female	Male	Male	Male
Race	Chinese	Malay	Chinese	Chinese	Chinese
Occupation	Pig farmer	Nurse	Veterinary assistant	Pig farmer	Pig farmer
No. of discrete, high signal-intensity lesions in MR imaging	5	>20	5	5	2

brain MR imaging and 10 other case controls with normal brain imaging and positive anti-Nipah antibody.

DISCUSSION

This study showed that 16% of patients with asymptomatic Nipah virus infection had subclinical cerebral involvement in MR imaging. Although the appearance in the MR imaging lesions among the asymptomatic subjects were similar to that of acute Nipah encephalitis, they were less numerous. These lesions were likely to also reflect the pathological processes of widespread vasculitis-induced thrombosis and microinfarcts seen in the fatal cases.[1,8] In addition to the antibody response during the acute infection, the virus also caused widespread vasculitis-induced thrombosis and microinfarcts. However, unlike patients with acute Nipah encephalitis, the lesions were less in numbers and not severe enough to produce clinical

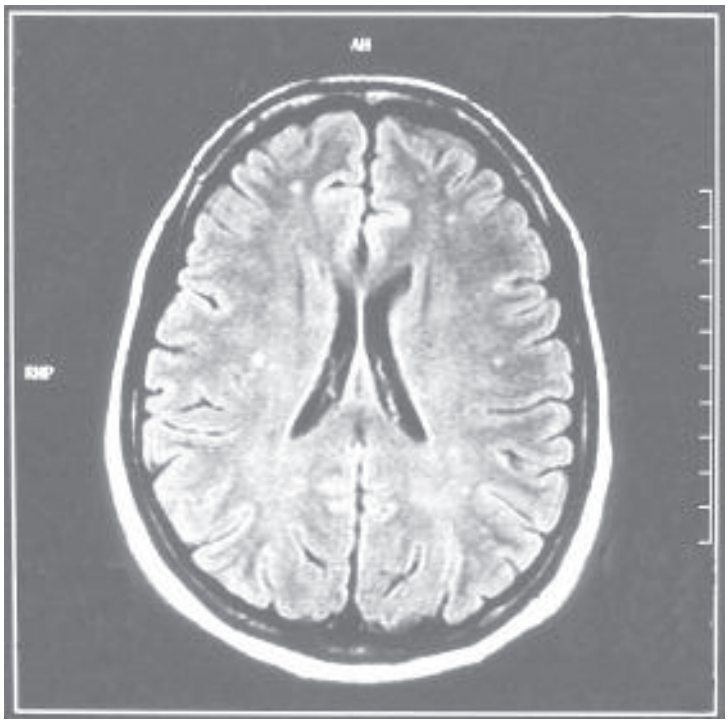

Figure 1: 41 years old nurse with asymptomatic Nipah virus infection. Axial fluid attenuated inversion recovery MR image shows multiple discrete lesions in subcortical and deep white matter of cerebrum.

symptoms. None of the subjects have underlying diabetes mellitus and hypertension. In view of the subjects' age and lack of atherosclerotic risk factors, though not excluded, the lesions are unlikely to be due to "unidentified bright objects" (UBO).

This study also showed that the degree of exposure to the sick animals did not affect the likelihood of cerebral involvement among the asymptomatic patients. This is consistent with the observation that in acute Nipah encephalitis, high exposure to sick animals was not a significant risk factor for mortality (personal communication: HT Chong, University Malaya Medical Centre). On the other hand, the degree of exposure to sick animals do affect the likelihood of developing symptomatic Nipah virus infection.[5-7] This indicates that viral load is important in determining the likelihood of an exposed subject to develop the infection. However, once infected, the severity of disease appeared to be dependent on host factors.

Nipah encephalitis is unique in that some patients may have relapse encephalitis after acute encephalitis. There were other patients who developed late-onset encephalitis a period following the initial exposure to the virus. The MR imaging and histopathology suggested a process of focal encephalitis in those patients with relapse encephalitis and late-onset encephalitis.[3,8] This MR imaging study on asymptomatic Nipah virus infection has demonstrated cerebral abnormalities in 16% of the subjects. This suggests that in the patients with late-onset encephalitis, the virus may have entered the brain during the initial infection when the vasculitis-induced thrombosis and microinfarcts occurred. As reported earlier, late-onset encephalitis may occur in patients whose initial cerebral MR imaging was normal.[8] MR imaging, though sensitive in detecting vasculitis-induced thrombosis and microinfarcts, may not be sensitive enough to reflect all the microinfarcts. In acute Nipah encephalitis, the number of microinfarcts lesions in necropsy far outnumber the lesions seen in MR imaging (personal communication: KT Wong, University Malaya Medical Centre). Thus, vasculitis-induced thrombosis and microinfarcts may occur in subjects with asymptomatic Nipah virus infection, despite normal cerebral MR imaging.

We have previously also demonstrated the lack of correlation between the numbers of discrete, high signal lesions seen in MR imaging and severity of infection. The severity of disease may be due to the degree of direct neuronal involvement which is not reflected in MR imaging.[8,10]

The Intensive Care Nurse who helped to care for patients with acute Nipah encephalitis, and who subsequently developed asymptomatic Nipah virus infection and abnormal cerebral MR imaging showed that human-to-human transmission of the infection is possible. One other nurse with asymptomatic Nipah virus infection had normal cerebral MR imaging. Nipah virus has been isolated from the upper respiratory secretions and urine in 8 out of 20 patients with acute Nipah encephalitis.[11] In these hospital acquired cases, the possible modes of transmission was the infected respiratory droplets and urine.

The abnormal cerebral MR imaging in patients with asymptomatic Nipah virus infection is another unique feature of the Nipah virus infection, not seen in other viral encephalitis.

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