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Late-onset Nipah virus encephalitis 11 years after the initial outbreak: A case report

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Abstract

Nipah virus infection is known to cause late-onset and relapsed encephalitis, in addition to an acute encephalitic illness. This is a report of a 35 years old woman, who had exposure to the Nipah virus infection during the 1999 Malaysian outbreak, was positive for Nipah IgG by immunofluorescence, and had multiple small hyperintense lesions in brain MRI typically seen in acute Nipah encephalitis patients, indicating asymptomatic Nipah virus infection. She subsequently developed acute encephalitis after 11 years, manifesting as diplopia, internuclear opthalmoplegia and epileptic seizures with pleocytosis in cerebrospinal fluid examination. She had another episode of relapsed encephalitis a year later, with seizures, memory impairment, chorea and new lesions in MRI brain. This patient is unusual in the long incubation of 11 years before manifesting with late-onset Nipah encephalitis.

INTRODUCTION

Nipah virus, a single stranded RNA virus of the genus *Henipavirus*, was first discovered in 1999 when it caused an encephalitis outbreak in the pig-farming community in Malaysia.[1,2] During this initial outbreak, 265 patients had acute encephalitis, with 105 fatalities.[1-3] Another 89 patients had either non-encephalitic illness or asymptomatic infection.[4,5] Fruit bats of the *Pteropus* family were found to be the reservoir of the virus and are known to have a wide distribution across Asia.[6] The virus probably caused infection in pigs through their consumption of contaminated fruits half eaten by bats, and the virus subsequently spread to humans in direct contact with pigs.[1-3] Since 2001, recurrent outbreaks of Nipah encephalitis have been reported in Bangladesh and North Eastern India, where transmission was directly from bats to humans, and humans to humans.[7]

One unusual feature of Nipah virus infection was the occurrence of relapsed and late-onset encephalitis. Relapsed encephalitis was when the patient manifests neurological disease after recovery from acute encephalitis. Late-onset encephalitis was the appearance of neurological manifestations for the first time more than 10 weeks after the initial exposure. They were reported to occur in 9% and 5% of patients respectively in the Malaysian outbreak.[4,5] There were clear differences in the clinical manifestations, imaging changes and pathology of relapsed and late-onset encephalitis as compared to acute Nipah encephalitis. Acute Nipah encephalitis manifested as a diffuse encephalitic syndrome with fever and altered consciousness. The MRI brain showed multiple, disseminated, small discrete hyperintense lesions reflecting microinfarcts due to vasculitis of small vessels. Pathology showed evidence of systemic involvement with vasculitis seen also in the lung, spleen and heart. On the other hand, relapsed and late-onset Nipah encephalitis usually presented with seizure and focal neurological deficits without involvement of organs other than brain. MRI showed confluent cortical involvement, and necropsy shows focal encephalitis.[4,5] Delayed neurological deterioration was also seen after acute Nipah encephalitis in Bangladesh[8], and relapsed encephalitis has also been reported in the related Hendra virus infection.[9]

We report of a patient who had close contact with family members with acute Nipah encephalitis during the 1999 outbreak, but was asymptomatic then. She subsequently developed late-onset encephalitis after an interval of 11 years.

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CASE REPORT

Our patient is Chinese woman who was 24 years old when the Nipah encephalitis outbreak occurred in 1999. Although her family had stopped pig farming and moved away from the Bukit Pelanduk outbreak area 10 years before the outbreak, she had returned to visit her uncle and aunt with Nipah encephalitis, and her aunt subsequently passed away from the illness. However, she did not come into contact with pigs or other domestic animals. She remained well during the outbreak.

In 2007, at the age of 32 years, she complained of dizzy spells for which she consulted an ENT specialist. An MRI of the brain showed multiple small white matter hyperintensities in the cerebral subcortical and deep white matter on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences. (Figure 1). She was managed symptomatically and improved.

In March 2010, at the age of 35 years, she noticed diplopia and in June, she developed multiple episodes of epileptic seizures, often during sleep. The seizures were preceded by an aura of bad smell, followed by paraesthesia ascending from the right leg. Her face could be pulled to one side and there was impairment of consciousness. She sought treatment then at another hospital, where she was clinically found to have nystagmus and right internuclear opthalmoplegia. Another MRI of the brain done in July 2010, again showed multiple discrete high signal intensity lesions scattered in both subcortical and deep white regions without any enhancement (Figure 2). Cerebrospinal fluid (CSF) examination showed pleocytosis (68 white blood cells (WBC)/ μl, predominantly lymphocytes), elevated protein level of 0.66 g/l, and normal glucose level. There were no oligoclonal bands detected. Her symptoms improved subsequently.

In June 2011, she presented to our hospital for consultation after her husband noted deterioration of her memory over the previous 2 months, as she kept asking the same questions repeatedly. There was excessive involuntary body and limb movement. On examination, she had bilateral horizontal gaze-evoked nystagmus and chorea involving the limbs and neck. MRI brain showed new confluent hyperintensities on T2-weighted sequences over both anterior temporal lobes involving the cortex and white matter, while the previously noted white matter lesions remained the same (Figure 3). CSF examination showed a WBC count of 10/μl, but normal protein (0.33 g/l) and glucose levels. Screening for connective tissue disease and serological tests for HIV, Herpes and Japanese encephalitis infections were negative. Serum Nipah IgG test was positive, but IgM negative by immunofluorescence assays (IFA). The virus could not be isolated from the CSF.

She was treated symptomatically and the seizures reduced in frequency on levetiracetam

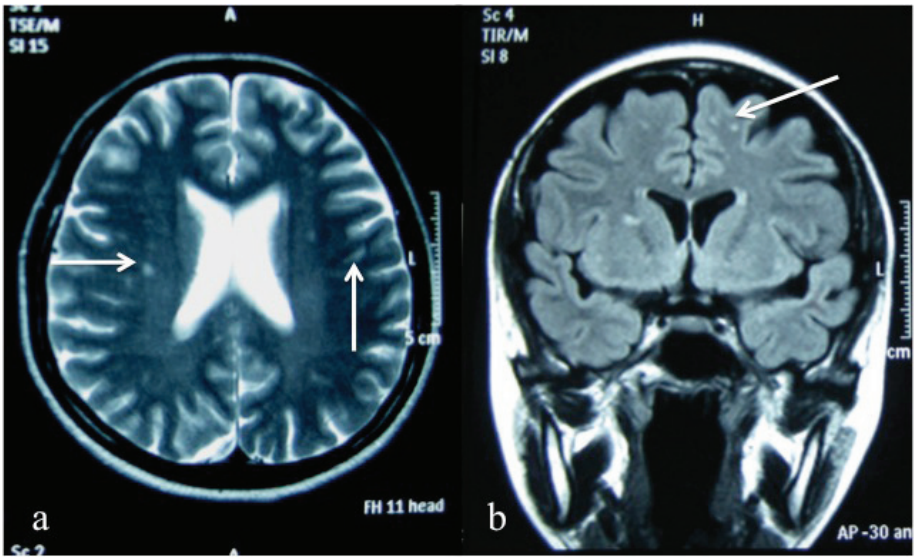

Figure 1: Magnetic resonance imaging (MRI) in 2007 when the patient had dizzy spells, before the onset of definite neurological illness. a) Axial T2W and b) coronal FLAIR of the brain showing non-enhancing multiple hyperintensities in the subcortical and deep white matter of the parietal lobes (white arrows) probably from asymptomatic Nipah virus infection in 1999.

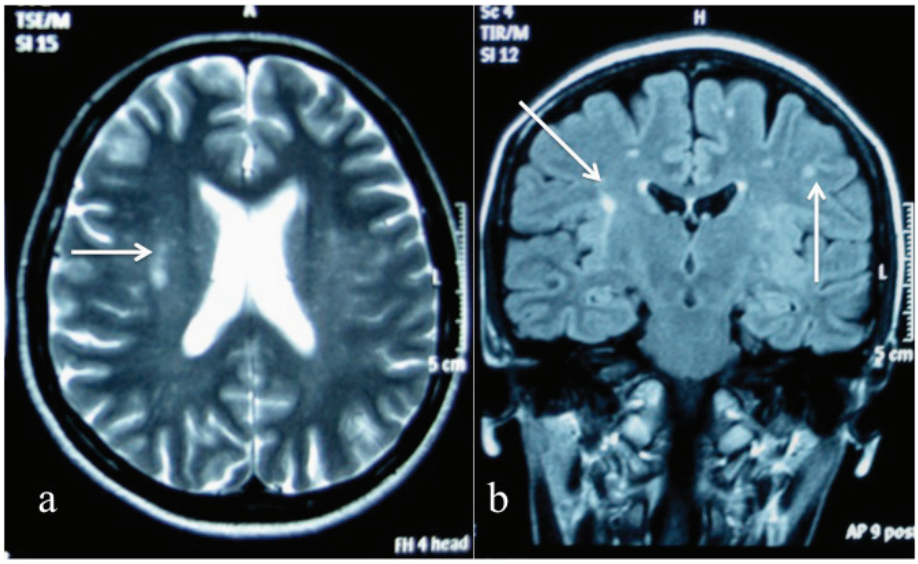

Figure.2: MR imaging in July 2010 after the development of brain stem sign, seizures and CSF pleocytosis from late-onset encephalitis. a) Axial T2W and b) coronal FLAIR showing increasing number of white matter hyperintensities (white arrows), some of which was slightly larger in the right corona radiata. No enhancement was demonstrated on post contrast images. Both temporal lobes appeared unremarkable.

500mg BD. On her last review in December 2011, her chorea and memory have also improved.

DISCUSSION

We report a patient with asymptomatic Nipah virus infection during the 1999 outbreak of acute Nipah encephalitis in Malaysia and subsequently developed late-onset Nipah encephalitis. We believe that she had Nipah infection during the outbreak because of likely exposure to the virus during her contact with ill relatives, her MRI showing the typical multiple, disseminated, discrete hyperintense lesions (Figure 1), and her

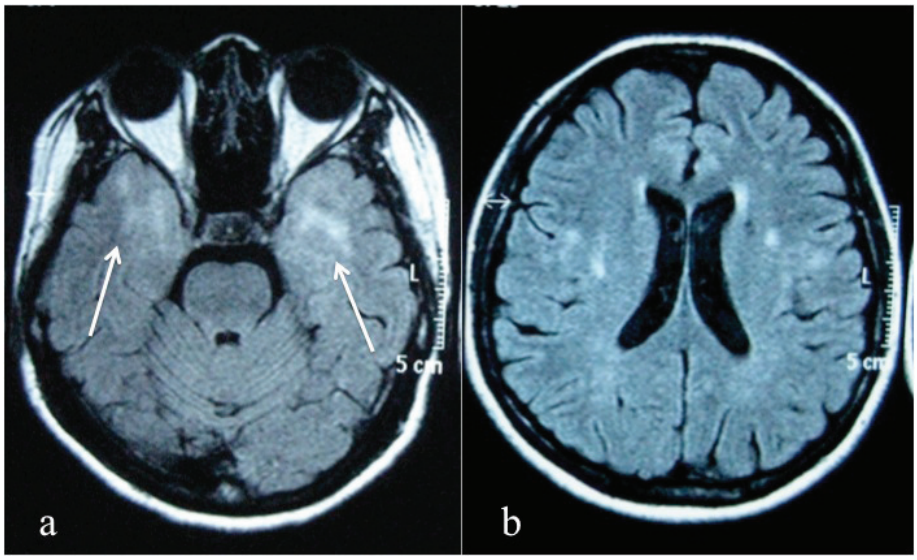

Figure 3: MRI axial FLAIR images (a , b) done in June 2011 following new symptoms of memory impairment and chorea from relapsed encephalitis. a) There were new confluent hyperintense lesions located at anterior temporal lobes bilaterally affecting the white matter and cortex (white arrows). b) The previously seen white matter lesions in the fronto-parietal lobes had remained unchanged in appearance.

positive Nipah serology.[10,11] The MRI brain lesions are unusual at her age, and she did not have other illnesses that could account for such lesions. As she had no direct contact with pigs, we believe she was infected by direct human-to-human spread, which although common in the Bangladesh and Indian Nipah encephalitis outbreaks[12,13], was unusual in the Malaysian outbreak.[11,14]

She developed an encephalitic illness 11 years later, between March to June 2010, when she presented with neurological symptoms of diplopia, internuclear opthalmoplegia, epileptic seizures, as well as having raised CSF white blood cells and protein. As there were no other causes of encephalitis found, and in view of the past history of asymptomatic Nipah virus infection, we now attribute her illness to late-onset Nipah encephalitis, although this was not suspected at that time.

This patient is remarkable as late-onset Nipah encephalitis occurred 11 years after the initial infection, the longest period of delay reported to date. Previously the longest duration of late-onset Nipah encephalitis was in a husband and wife who developed the illness 53 months after the initial infection.[5] Such long incubation is also seen in measles, another paramyxovirus which causes subacute sclerosing panencephalitis.

She had a relapsed encephalitic illness close to a year later between April to June 2011, with new symptoms and signs of memory impairment and chorea, CSF showing borderline raised while cell count 10/μl, positive Nipah IgG serology, and brain MRI showing new lesions with hyperintensities in both anterior temporal lobes. The virus could not be isolated because it is likely that viral replication was defective and very few virus particles matured. However, the progression of infection as evidenced by new lesions in the brain suggests either cell to cell spread of infection[15] or immune-mediated injury. We attributed the illness to relapsed Nipah encephalitis. Such a second neurological episode was seen in 3 out of 24 (13%) relapsed and late-onset Nipah encephalitis patients in our previous study.[4]

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