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Relapsed and late-onset Nipah encephalitis, a report of three cases

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Abstract

The Nipah virus that caused a fatal outbreak among Malaysian pig-farmers in 1998-1999 was known to cause relapsed and late-onset encephalitis. We report 2 patients with relapsed and one patient with late-onset encephalitis up to 53 months after the initial infection. Two of the patients were husband and wife and they developed relapsed and late-onset encephalitis within 5 days of each other. This report suggests that Nipah virus could cause relapsed and late-onset encephalitis after lying dormant for more than 4 years. Environmental factor could be important in precipitating the relapsed and late-onset encephalitis, perhaps by transiently suppressing the immune system.

INTRODUCTION

Nipah virus caused severe acute encephalitis with high mortality among pig farmers during an outbreak in Malaysia in 1998 – 1999.[1-7] Nipah virus infection present clinically mainly as acute encephalitis, with short incubation period of less than two weeks, with fever, headache, giddiness followed by coma. Distinctive clinical signs include segmental myoclonus, areflexia and hypotonia, hypertension and tachycardia. The mortality was 32 – 41%. Some 40 – 53% of patients recovered fully, with 15 – 19% having persistent neurological deficits.[3,4] Nipah virus infects the endothelial cells, leading to syncytial formation and necrosis of these cells, thus causing a systemic vasculitis with extensive thrombosis, resulting in parenchymal necrosis, the most important site being the central nervous system.[6] The virus also affects the neurons directly, explaining the distinctive neurological features.[3] Subsequently it was reported that 12 out of the 160 (7.5%) survivors and 10 of the 89 (3.4%) non-encephalitic or asymptomatic patients developed a relapsed and late-onset Nipah encephalitis up to 24 months after the initial outbreak. These patients presented with fever, headache, seizure and focal neurological deficits, with a mortality of 18%. MR imaging showed patchy areas of confluent cortical lesions. In between the acute infection and the relapses the patients were well. Necropsy of 2 cases showed changes of focal encephalitis with positive immunolocalization for Nipah virus antigen, but without vasculitis, the hallmark of acute Nipah infection and perivenous demyelination. It was believed that the relapsed and late-onset encephalitis represented rapid viral replication in the brain parenchyma, after a quiescent period.[8] This is a report of 2 other patients with acute Nipah encephalitis and one patient with nonencephalitic Nipah virus infection during the initial outbreak, who later developed relapsed and late-onset Nipah encephalitis, up to 4 + years after the outbreak.

CASE REPORT 1

This 23 years old male was first admitted to University Malaya Medical Centre on 27th February 1999. He was a pig farmer from the Nipah encephalitis outbreak area, Sungai Nipah. He has a cousin, a pig farmer, who was admitted two weeks later and died from acute Nipah encephalitis. He presented with 3 days history of fever, headache, dizziness and generalized body ache. At presentation, he was flushed in appearance, had fever of 39^{O}C, tachycardia of 114 beats per-minute, hepatomegaly of 2 finger-breath below costal margin. He was conscious and rational, with no neck stiffness and neurological deficits. He has previously health, a non-smoker and a social drinker. On investigation, the full blood counts, renal and liver function tests were all normal. Lumbar puncture done on the next day showed an opening pressure of 8 cm H_2O, with 10 red blood cells, 30 white blood cells per-µl with 60% lymphocytes, 40% polymorphs; protein of 0.79 g/l, and glucose of 3.2 mmol/l. Gram stain and cryptococcal antigen were negative. Cerebrospinal fluid examination repeated showed 208 white cells per-µl with

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90% lymphocytes. He developed neck stiffness and increased drowsiness on 4th days after admission. He was diagnosed as acute Nipah encephalitis and was given general supportive treatment but not anti-viral agent. He had an uneventful recovery and was discharged after 9 days. The anti-Nipah antibody was positive in the serum for IgM, and negative for IgG. He did not go back to pig farming but worked as a plumber after this illness.

He presented again on 5th July 2002 with 2 episodes of generalized tonic-clonic seizure on 30th June 2002, some 40 months after the initial acute encephalitis. The first seizure lasted 5 minutes with the second seizure occurring 3 hours later. There was also 2 days history of fever and lethargy preceding the seizure, transient weakness of right hand, slowness in answering questions, and speaking less. On examination, he was afebrile with normal pulse, blood pressure and systemic examination. He was conscious and rational, with no abnormal neurological sign. The full blood count, renal and liver function tests were all normal. Brain MR imaging showed confluent areas of hyperintensities in both frontal lobes in fluid-attenuated inversion recovery (FLAIR) sequences, right more than left. Electroencephalography (EEG) showed bifrontal slow wave, right more than left, with infrequent left temporal discharge. The photic stimulation response was attenuated on the left side. The anti-Nipah antibody was positive in the serum for IgG, and negative for IgM. He remained well and was seizure-free during his stay. He was diagnosed as relapsed Nipah encephalitis and was treated with ribavirin and sodium valproate 200 mg tds per-oral. He was discharged well on 10th July 2002. The patient was last seen on 8th July 2003 when he remained well, having stopped his sodium valproate in June 2003. He was seizure-free since discharge from hospital.

CASE REPORT 2

This 51 years old pig farmer from Bukit Pelanduk, a Nipah encephalitis outbreak area, was admitted to Seremban Hospital on 31st March 1999. He presented with one week history of fever, headache, sore throat, anorexia, nausea, vomiting, arthralgia, dizziness and drowsiness. On examination, other than being febrile, he had no other abnormal signs. The liver, renal function tests and other systemic investigations were normal. The anti-Nipah antibody was positive in serum for both IgM and IgG. He refused cerebral spinal fluid examination. He was diagnosed to have non-encephalitic Nipah virus infection and was given a week's course of oral ribavirin. He did not go back to pig farming, but worked as building contractor after this illness.

He remained well until September 2003, some 53 months later. He had fever on 1st September with headache and left sided weakness. On 5th of September, he developed an episode of epileptic seizure involving left limb followed by generalized tonic-clonic convulsion. There were a few further episodes of seizure after that. He was admitted into two private medical centres and Seremban Hospital in turn before transferring to University Malaya Medical Centre on 15th September. On examination, he was febrile, drowsy, was orientated to time, place and person, but was slow in response to oral questions. There was left hemiparesis with strength of 3/5 Medical Research Council (MRC) scale. The plantar responses were flexor bilaterally with hyporeflexic tendon reflexes.

CT brain scan was normal. Initial EEG showed right fronto-central repetitive sharp waves. A repeat EEG at 3rd week of illness showed right frontal delta and diffuse theta waves with no sharp waves. MR imaging showed confluent areas of hyperintensities in right hippocampus, posterior parietal, medical temporal and operculum in FLAIR and T2-weighted sequences. The anti-Nipah antibody was positive in serum for both IgM and IgG. Chest radiograph showed diffuse fluffy consolidation bibasally. He was diagnosed to have late-onset Nipah encephalitis with secondary aspiration pneumonia. He was treated with ribavirin, phenytoin and carbamazepine, ceftriaxone and metronidazole. He gradually improved. About a month after the illness, there was persistent mild weakness of the right upper limb only.

CASE REPORT 3

This 43 years old pig farmer was the wife of Case 2. She was first admitted to Seremban hospital on 19th April 1999 with fever, anorexia, myalgia and generalised weakness. She deteriorated after admission to hospital, and developed reduced consciousness, myoclonus of facial muscles, and upper limb dystonia. The anti-Nipah antibody was positive in serum for both IgM and IgG. She was treated with oral ribavirin and was ventilated for 4 days. She recovered after 3 weeks and was discharged well without neurological deficits. After the illness, she did not go back to pig farming and remained as a housewife.

On 5th September 2003, she presented to Seremban hospital with a single episode of nocturnal generalized tonic-clonic seizure. On examination, she was afebrile, but had hyperreflexia of the left limbs. She was discharged after 24 hours. There was no abnormal signs when she was reviewed in University Malaya Medical Centre on 18th October 2003. EEG done on the same day showed bifrontal delta waves with right preponderance, right fronto-temporal sharp and sharp-and-slow-waves. MRI brain with FLAIR sequence showed confluent areas of hyperintensities in right mesial temporal area extending to the adjacent insular region. There were similar, though smaller lesions in the opposite mesial temporal region. There was a small deep white matter hyperintensity consistent with previous acute Nipah encephalitis. The anti-Nipah antibody was positive in the serum for IgG and negative for IgM. The patient remained well after this illness.

DISCUSSION

This 3 patients shows similar clinical and clinical features as other relapsed and late-onset Nipah encephalitis.[8,9] All 3 patients were well after the acute Nipah encephalitis and non-encephalitic Nipah infection. They presented with a self-limiting acute illness, 2 with fever. The manifestations were mainly neurological. All 3 patients had seizures, 2 had mental change (Cases 1, 2), and two had focal neurological signs (Cases 2, 3). In the previous report involving 22 patients, 20 patients (91%) had acute onset of illness. The common clinical features were: fever (46%), headache (42%), seizures (50%), and focal neurological signs (42%). The disease plateau within 3 weeks and then improved, the mortality was 18%.[8] The MR imaging findings were also similar to the previous reports, showing confluent cortical lesions, best seen in FLAIR sequences.[8,9] The EEG showed focally predominant show waves and sharp waves, corresponding to MRI and clinical lesions.[8] All the 3 patients had IgG anti-Nipah antibody, Case 1 also had IgM anti-Nipah antibody. In the previous report, anti-Nipah antibody was positive in serum for IgG in all of the 22 patients, and for IgM in 10 of 22 patients (45%).[8]

With the previous 12 cases at 24 months[8], with the inclusion of Cases 1 and 3, there were a total of 14 cases of relapsed Nipah encephalitis more than 48 months after the outbreak. As there were 160 patients who survived acute encephalitis[2], the prevalence of relapsed encephalitis more than 48 months after the outbreak was about 9%. Similarly, with the previous 3 cases at 24 months, with the inclusion of Case 2, there were a total of 4 cases of late-onset Nipah encephalitis more than 48 months after the outbreak. As there were 89 patients previously known to have nonencephalitic or asymptomatic Nipah infection[8], the prevalence of late-onset encephalitis more than 48 months after the outbreak was 5%. However, there was a reduction in the frequency of relapsed and late-onset Nipah encephalitis with the progression of time, with 22 cases at up to 24 months after the outbreak, as compared to 3 cases at the third and fourth year after the outbreak.

It is remarkable that Cases 2 and 3, who were husband and wife, should both relapsed at about the same time more than 4 years after the initial outbreak. Previous study has shown that the involvement of relapsed and late-onset Nipah encephalitis was limited to the brain. Viral culture attempted from tracheal secretion, urine and nasal secretion were also negative.[8] The manifestation of both cases were that typical of relapsed and late-onset Nipah encephalitis rather than acute Nipah encephalitis. The outbreak of relapsed and late-onset Nipah encephalitis between the husband and wife was thus unlikely to be due to human-to-human spread of infection. This suggests that environmental factors could have triggered rapid replications in the virus persistent in the patients, causing focal encephalitis, perhaps by transiently suppressing the host immune response, though the exact nature of which is uncertain. In herpes zorster, which can cause recurrent neuritis, impaired immunity is an important factor in virus reactivation.[10]

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