REVIEW

Lessons from the Nipah virus outbreak in Malaysia

Lai-Meng LOOI MD, FRCP, Path and Kaw-Bing CHUA* MD, FRCP, Path

Department of Pathology, University of Malaya and *National Public Health Laboratory, Ministry of Health, Malaysia

Abstract

The Nipah virus outbreak in Malaysia (September 1998 to May 1999) resulted in 265 cases of acute encephalitis with 105 deaths, and near collapse of the billion-dollar pig-farming industry. Because it was initially attributed to Japanese encephalitis, early control measures were ineffective, and the outbreak spread to other parts of Malaysia and nearby Singapore. The isolation of the novel aetiological agent, the Nipah virus (NiV), from the cerebrospinal fluid of an outbreak victim was the turning point which led to outbreak control 2 months later. Together with the Hendra virus, NiV is now recognised as a new genus, Henipavirus (Hendra + Nipah), in the Paramyxoviridae family. Efforts of the local and international scientific community have since elucidated the epidemiology, clinico-pathophysiology and pathogenesis of this new disease. Humans contracted the infection from close contact with infected pigs, and formed the basis for pig-culling that eventually stopped the outbreak. NiV targeted medium-sized and small blood vessels resulting in endothelial multinucleated syncytia and fibrinoid necrosis. Autopsies revealed disseminated cerebral microinfarctions resulting from vasculitis-induced thrombosis and direct neuronal involvement. The discovery of NiV in the urine and saliva of Malaysian Island flying foxes (Pteropus hypomelanus and Pteropus vampyrus) implicated these as natural reservoir hosts of NiV. It is probable that initial transmission of NiV from bats to pigs occurred in late 1997/early 1998 through contamination of pig swill by bat excretions, as a result of migration of these forest fruitbats to cultivated orchards and pig-farms, driven by fruiting failure of forest trees during the El Niño-related drought and anthropogenic fires in Indonesia in 1997-1998. This outbreak emphasizes the need for sharing information of any unusual illnesses in animals and humans, an open-minded approach and close collaboration and co-ordination between the medical profession, veterinarians and wildlife specialists in the investigation of such illnesses. Environmental mismanagement (such as deforestation and haze) has far-reaching effects, including encroachment of wildlife into human habitats and the introduction of zoonotic infections into domestic animals and humans.

Key words: Nipah, encephalitis, El Niño, haze, deforestation, pig, bat, zoonosis

INTRODUCTION

The Nipah virus outbreak in Malaysia (1998/1999) and its subsequent spread to Singapore caught both countries relatively unprepared. In Malaysia, it caused tremendous human suffering and near total collapse of the billion-dollar pig-farming industry. The discovery of the novel Nipah virus was a significant turning point in the control of this outbreak. The outbreak was swiftly brought under control with the assistance of international scientific partners. This paper recapitulates the salient features of the outbreak and the main lessons that have been learnt from it.

Chronology of the outbreak

In late September 1998, an outbreak of human acute febrile encephalitis with high fatality occurred in pig-farms in the suburb of Ipoh, Perak in Peninsular Malaysia. This was preceded by the occurrence of respiratory illness and encephalitis in pigs. The outbreak was initially attributed to Japanese encephalitis (JE) because 4 serum samples from 28 patients in this outbreak area tested positive for JE-specific IgM (subsequently confirmed by the WHO Collaborating Center for Tropical Disease at the University of Nagasaki, Japan) and JE nucleic acids were detected in some
of the patients’ sera by reverse-transcriptase PCR carried out at the Arbovirus Unit of the University of Malaya. Consequently, early control measures, including anti-mosquito foggings and vaccination of pigs against JE, were ineffective. The epicenter in Ipoh saw 15 fatalities, 9 of whom were subsequently confirmed to have Nipah virus infection at autopsy.

Unfortunately, pig-farmers affected by the outbreak sold pigs to other farms across the country. By February 1999, the outbreak had spread to Sikimat, Sungai Nipah Village and Bukit Pelandok (the largest pig-farming communities) in Negri Sembilan, some 300 km south of Ipoh. This second, and more severe, epicenter contributed some 180 patients and 89 deaths. With further surreptitious movement of infected pigs, cases also emerged from around Sepang and Sungai Buloh in Selangor. In March 1999, 11 cases, with 1 death, was reported among abattoir workers in Singapore who had handled pigs imported from Malaysia. By then the outbreak had caused nationwide public fear, and near collapse of the local pig-farming industry.

Healthcare workers looking after the patients had been convinced relatively early in the outbreak that this was not due to JE. Unlike JE, the illness affected adults rather than children, and many victims had previous immunisation against JE. The autopsy findings were not consistent with the usual findings in JE and suggested some other agent. A high proportion of victims had direct physical contact with pigs, unlike a mosquito-borne disease. Furthermore, ill pigs developed a severe barking cough and many died from the disease. However, conflicting governmental pronouncements that JE was the culprit delayed appropriate action for outbreak control. It was the isolation of the Nipah virus (NiV) from the cerebrospinal fluid (CSF) of an outbreak victim (from Sungai Nipah village) by a medical virologist at the University of Malaya in early March 1999, that brought acknowledgement that the infection was caused by an agent previously unknown to science. Together with the Hendra virus (HeV), the novel virus is now recognised as a new genus, Henipavirus (Hendra + Nipah), in the Paramyxoviridae family. It was shown that NiV and HeV shared enough epitopes for HeV antigens to be used in a prototype serological test for NiV antibodies. This helped tremendously in the subsequent screening and diagnosis of NiV infection.

The outbreak in Singapore ended with prohibition of importation of pigs from Malaysia and closure of abattoirs, and the outbreak in Malaysia ceased with widespread surveillance of pig populations, and the culling of over a million pigs. The last human fatality occurred on 27th May 1999. By then, 265 cases of acute NiV encephalitis with 105 deaths had been recorded in Malaysia, giving a mortality rate of nearly 40%.

Clinicopathological profile of Nipah virus encephalitis

The discovery of a highly infectious virus capable of high human fatality, brought Malaysia into sharp focus in the scientific world. The swift and ready assistance of international scientific colleagues (Centers for Disease Control and Prevention, USA; Commonwealth Scientific & Industrial Research Organisation, Australia and Singapore General Hospital) went a long way towards the rapid characterisation of the Nipah virus and the development of surveillance and control measures. Numerous scientific studies were initiated into the clinical, radiological and neurophysiological manifestations and the epidemiology, pathology and pathogenesis of this new disease and are on-going in Malaysia and throughout the world. The following are some of the landmark findings:

1. Close contact with infected pigs was the main mode of transmission to humans. This formed the basis for pig-culling that eventually stopped the outbreak.

2. Although the risk of nosocomial transmission of NiV appeared to be low in the Malaysian outbreak, demonstration of viral infectivity in human secretions initiated a rigorous barrier nursing protocol that was instituted throughout Malaysia to prevent human-to-human transmission. In subsequent NiV outbreaks in Bangladesh and India, human-to-human transmission caused substantial mortality among healthcare workers and family members. The barrier nursing protocol probably prevented similar tragedies in the Malaysian outbreak.

3. The main presenting features were fever, headache, dizziness and vomiting. More than 50% had reduced consciousness and prominent brain-stem dysfunction. Distinctive clinical signs included segmental myoclonus, areflexia and hypotonia,
hypertension and tachycardia, suggesting brain-stem and upper cervical cord involvement. A few patients developed atypical pneumonia.1,2

4. Autopsies were performed on 32 Malaysian outbreak victims (29 full, 3 limited to the brain).3 All were positive for NiV (either by immunohistochemistry or serology). The NiV appeared to target medium-sized and small blood vessels resulting in endothelial multinucleated syncytia and fibrinoid necrosis. Pathological lesions were mainly seen in the brain with disseminated microinfarction as a result of vasculitis-induced thrombosis and direct neuronal involvement. Vasculitic lesions were also detected in the respiratory tract, kidneys and heart. Autopsies on infected pigs revealed similar lesions in the respiratory tract and meninges.4

5. The incubation period in humans ranged from 4 days to 2 months, with more than 90% at 2 weeks or less. The rate of subclinical infection ranged from 8 to 15%.1

6. The mortality rate was close to 40%. The mean duration of illness from onset of symptoms to death was 16 days. Mortality was associated with positive viral culture from the CSF and severe brain-stem involvement.9

7. Serology with IgG and IgM antibody against Hendra (and later Nipah) antigens was developed as an aid to diagnosis. The presence of CSF virus-specific IgM was evidence of increased inflammatory activity but did not have a protective effect on the illness. Humoral immunity probably has a minor role to play in the disease process and recovery.9

8. Ribavirin treatment in acute NiV encephalitis was associated with 36% reduction in mortality and more survivors without neurological deficits.10

9. Follow-up of survivors (160 acute encephalitis patients and 89 nonencephalitis/asymptomatic infections) suggests that a unique relapsing and remitting encephalitis or late-onset encephalitis can result as a complication of persistent NiV infection in the central nervous system.11

10. The golden hamster was discovered to be a good infectious model, paving the way for successful experimental trials for various therapeutic agents.12

11. A novel approach to collection of urine from roosting Malaysian Island flying foxes provided the crucial evidence that fruitbats (Pteropus hypomelanus and Petropus vampyrus) were natural reservoir hosts of NiV, and excreted the virus in their urine and saliva.13,14 This simple yet effective approach illustrates the importance of understanding the habits of wildlife in the investigation of zoonosis.

12. Meteorological and agricultural data provided supporting evidence that NiV should be considered an emerging pathogen driven by the severe 1997-1998 El Niño Southern Oscillation (ENSO) event.15 ENSO-related drought exacerbated the anthropogenic fires in Indonesia (which destroyed approximately 5 million ha of forest through “slash-and-burn” cultivation) during the months of August, September and October 1997, creating the most severe haze ever known in SouthEast Asia. Haze-related flowering and fruiting failure of forest trees coupled with increasing deforestation probably drove the migration of forest fruitbats to cultivated orchards. In Ipoh, there were numerous orchards surrounding pig-farms and indeed many fruit trees actually overhung pigsties. It is probable that initial transmission of the NiV virus from bats to pigs occurred in late 1997/early 1998 through contamination of pig feed and water by bat excretions.

13. Close proximity of pigs in pig farms contributed to rapid pig-to-pig transmission. The pig proved to be a good amplifying host for the virus. However, other animals, including cat, dog and horse, have been reported to show evidence of infection. One victim caught the infection from his pet dogs who subsequent died from the disease.16

LESSONS FROM THE OUTBREAK

1. While political and governmental support are extremely important in bringing about effective and swift control measures in outbreaks, it is important that determination and announcement of the cause of outbreaks...
be left to trained professionals such as scientists and medical doctors. Conflicting announcements can hamper effective outbreak measures.

2. A new disease may resemble and thus be mistaken for a familiar one. The danger of preconceived ideas, of fitting a disease into an existing mould, and ignoring discrepancies, is well illustrated by the early phase of this outbreak. If not for medical doctors keeping an open mind on new possibilities, the novel virus would not have been discovered and the devastation from the outbreak would have been far more severe.

3. Free sharing of information and cooperation among scientists and medical doctors, both locally and internationally, was one of the most positive aspects of the outbreak. Without this willingness to share and help, the virus would not have been characterized so rapidly nor effective surveillance and control measures devised so quickly. It is noteworthy that the outbreak, which had raged for 6 months, was controlled 2 months after the discovery of the virus.

4. The pro-active decision by the Government of Malaysia to compensate pig-farmers for the loss of pigs was crucial in stopping the surreptitious smuggling of pigs out of outbreak areas, and acceptance of massive pig-culling in all affected communities.

5. Regulations should be imposed on the design of pig-farms and other farmed animals. Attention should be given to features that can minimise rapid spread of disease among farmed animals (e.g. crowding) and spread of disease to humans (e.g. handling procedures, protective gear and hygiene). Planting of fruit trees within farms which may attract bats and other wildlife into farms, should be avoided.

6. There should be frequent surveillance of the pig population for evidence of fresh infection. That aside, there should be sharing of information of any unusual illnesses in animals and humans, an open-minded approach and close collaboration and coordination between the medical profession, veterinarians and wildlife specialists in the investigation of such illnesses.

7. Almost 75% of emerging infectious diseases over the last century have been zoonoses, having jumped the species barrier to infect humans. The far-reaching effects of environmental mismanagement (such as deforestation and haze) cannot be overemphasised, as this can lead to encroachment of wildlife into human habitats and the introduction of zoonotic infections into domestic animals and humans.

8. The widespread prevalence of the NiV in bats in Bangladesh, Thailand and Cambodia, and the recent Nipah outbreaks in Bangladesh and India makes it likely that there will be more future outbreaks in Asia. Inter-governmental cooperation to prevent anthropogenic and environmental activities that can lead to its re-emergence is crucial.

REFERENCES


