Differences in epidemiologic and clinical features of Nipah virus encephalitis between the Malaysian and Bangladesh outbreaks

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Abstract

Since the initial outbreak of Nipah encephalitis in Malaysia in 1998, the virus has reemerged in Bangladesh and the adjacent Indian state of West Bengal since 2001. To date more than 470 patients have been affected with over 250 fatalities in total. Although the source of the virus is believed to be the Pteropus fruit bats both in Malaysia and Bangladesh, there are also significant epidemiological and clinical differences in the outbreaks occurring in these two regions. Epidemiologically, in the Bangladesh and India outbreaks, bat-to-human transmission through food and animal and human-to-human transmissions were the predominant modes, the outbreaks were on a smaller scale and they have recurred every year except 2002 and 2006. Clinically, the mortality was higher and respiratory manifestation was more prominent in the Bangladeshi and Indian patients compared with their Malaysian counterparts, which might reflect differences in care and medical practices. There remain however, important differences in clinical manifestations which are likely to be due to some genetic variations in the virus.

INTRODUCTION

Nipah virus, of the family Paramyxoviridae and the genus Henipavirus, is a zoonotic virus that causes outbreaks of fatal encephalitis. It was discovered in 1999 in Malaysia after an outbreak involving mainly pig farm and abattoir workers. The virus was believed to spread from Pteropus fruit bats, its natural hosts, to pigs; and having been amplified in pigs, subsequently spread to humans. The first outbreak occurred in the Kinta valley of peninsular Malaysia in September 1998, and in December of the same year, spread to the Bukit Pelanduk pig farms south of Kuala Lumpur. By the end of the outbreak in May 1999, it had spread to three states in peninsular Malaysia and neighboring Singapore, devastated a multimillion dollar pig farm industry, affected some 265 patients and eventually caused 105 deaths with some 10% of survivors suffered from relapsed disease more than 4 years later.

The outbreak, unfortunately, did not end there. In 2001, two outbreaks occurred in Meherpur, Bangladesh and in Siliguri, neighboring West Bengal state, India. This was followed by outbreaks in Naogaon (2003), Rajbari and Faridpur (2004), Tangail (2005), Thakurgaon and Kushtia (2007), Manikgonj and Rajbari in 2008, all in Bangladesh. There are many similarities between the outbreaks in Bangladesh and India, and that in Malaysia/Singapore, both resulting in acute fatal encephalitis, and the reservoir of the virus is from the Pteropus fruit bats. There are substantial differences as well, especially in the epidemiology and clinical features of the disease.

EPIDEMIOLOGY

The most obvious and perhaps most important epidemiologic difference in the Malaysian and the Bangladesh/Indian outbreaks is the fact that whereas the disease spread mainly from pig-to-human in the Malaysian outbreak, bat-to-human through food or animal and direct human-to-human transmissions were the prominent modes of transmission in Bangladesh and India.

In the Malaysian outbreak, though bats were the reservoir of the virus, it was realized very early on that commercially farmed pigs were the main amplifying hosts resulting in the animal-to-human transmission. Even though the virus was found in the respiratory secretion and urine of the patients, screening of more than 338 health care workers with serology and magnetic resonance

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The second difference is that the outbreak and goats were allowed to roam freely. Large involved small herds. Animals such as cows rearing of other animals in Bangladesh often outbreak. 2.4 millions, contributed to the extent of the outbreak had a standing pig population of about size and high density nature of the commercial high infectivity to other pigs and humans. The their infected secretions probably underlies the prominent pulmonary illness among pigs with then acted as amplifying hosts and transmitted the virus spread rapidly among pigs, which due to the fact that in the Malaysian outbreak, 66 patients. in Siliguri, West Bengal, India, which involved 4 to 36 patients, with the largest outbreak in Bangladesh occurred during the winter months when the date palm juice was harvested gave support to the consumption of date palm juice causing the outbreak. 25 Other risk factors found to be significant in case control studies were contact with sick cows, contact with a herd of pigs, and climbing trees. 25 The possible reasons for the difference include differences in the genetic make-up of the different strains of virus involved in these outbreaks with more prominent pulmonary disease and infective secretions in Bangladesh and Indian patients, and the use of barrier nursing technique among Malaysian health care workers early in the outbreaks might contributed to prevent person-to-person transmission. 21 It is also possible that the bats shed a higher amount of viable viral particles into the date palm juice through secretions than on the partially eaten fruit. 25 This, however, remains to be proven.

The second difference is that the outbreak in Malaysia/Singapore was on a much larger scale than subsequent ones in Bangladesh and India. There were 265 patients admitted with 105 fatalities in the Malaysian outbreak. 4 The outbreaks in Bangladesh and India were smaller involving 4 to 36 patients, with the largest outbreak in Siliguri, West Bengal, India, which involved 66 patients. 8 18 The reason for this is perhaps due to the fact that in the Malaysian outbreak, the virus spread rapidly among pigs, which then acted as amplifying hosts and transmitted the virus to the farm workers and owners. The prominent pulmonary illness among pigs with their infected secretions probably underlies the high infectivity to other pigs and humans. The size and high density nature of the commercial pig farm industry, which at the time before the outbreak had a standing pig population of about 2.4 millions, contributed to the extent of the outbreak. 25 29 In contrast, the pig farming and rearing of other animals in Bangladesh often involved small herds. Animals such as cows and goats were allowed to roam freely. Large scale animal to animal spread of disease was thus unlikely. The outbreaks in Bangladesh and India were believed to occur from bat-to-human through food and animals and human-to-human transmission without an intermediate amplifying host. In fact, an extensive search has found no other animal reservoir of the virus in Bangladesh. 9

Thirdly, the outbreaks in Bangladesh and India recur almost annually, while in Malaysia the outbreak has not recurred for the past 10 years. 8-16,30 The outbreaks in Bangladesh and India also occurs in widely separated geographical areas, often simultaneously. 10,12 Since bats are the only reservoirs, this signifies frequent introduction of the virus from bats to humans. This difference could be explained by the much larger Pteropus fruit bat population in Bangladesh, and the close proximity between human and bats habitat in many of the rural villages in Bangladesh. The practice of consuming raw date palm juice, which is believed to be an important mode for the virus to spread from bats-to-human through food in Bangladesh, is not a custom in Malaysia. On the other hand, there has been active campaign to discourage planting of fruit trees at the vicinity of pig farms since the last outbreak in Malaysia.

CLINICAL FEATURES

The most pronounced difference in the clinical expression of Nipah virus infection in the outbreaks of the two geographical regions is that in the initial outbreak in Malaysia, respiratory involvement was not the dominant feature, and was seen in 14-29%, although 2 out of 11 patients in the same outbreak among abattoir workers in Singapore presented with pneumonia without encephalitis. 31 In the outbreaks in Bangladesh however, cough and respiratory difficulty occurred in 62% and 69% of the patients, with chest radiographs of some patients showing diffuse bilateral opacities covering the majority of lung fields consistent with acute respiratory distress syndrome. 17 In the outbreak in Siliguri, India, respiratory symptoms was reported in 51% of patients. 10 The prominent respiratory involvement, and the relative lack of implementation of infection control practices probably underlies the human-to-human transmission in the Bangladesh and Indian outbreaks. 16,20 The difference in the genetic make-up of the viral strains is probably the explanations for the difference in the clinical manifestations between the two regions, with prominent lung involvement in the Bangladesh and India patients. 16,27
The second important difference is the relatively high mortality rate in the Bangladesh and Indian outbreaks. In the Malaysian outbreak, mortality varied from 32 – 41%, whereas in the Bangladesh and Indian outbreaks mortality varied from 33 – 100%. Overall, in Bangladesh and India from 2001 to 2008, there were 206 patients affected with 73% case fatality.\textsuperscript{2,5,8-16,18,30} The difference in mortality may be attributed to the difference in the health care facilities; there is lack of adequate health care in Bangladesh compared to the urban intensive care setting in Malaysia.\textsuperscript{15,17} Additionally ribavirin was used in the Malaysian outbreak\textsuperscript{12}, as well as the fact that most of the patients in Malaysia were healthy adult male\textsuperscript{2,5}, as compared with higher proportion of younger and older patients in Bangladesh and India.\textsuperscript{8,10,11,13,14,17} The different strains of virus found in these two regions may also have different virulence and contributed to differences in mortality rates.

The other important difference in clinical manifestation is that the dramatic, persistent, segmental myoclonus seen in 32 – 54% of patients in the Malaysian outbreak\textsuperscript{2,5} was not observed in the patients from Bangladesh and India, even though generalized hyporeflexia, common in Malaysian patients\textsuperscript{2,5} was also noted in the Bangladesh outbreaks.\textsuperscript{17} During acute encephalitis, discrete high-signal-intensity lesions, measuring 2-7 mm, disseminated throughout the brain, mainly in the subcortical and deep white matter of the cerebral hemisphere were seen in MR imaging of all the Malaysian patients. The changes were thought to reflect widespread microinfarctions from underlying vasculitis of cerebral small vessels.\textsuperscript{2} These changes were not observed in the MR imaging of the limited number of Bangladesh patients during acute encephalitis. Instead the changes were confluent high signal lesions involving both gray and white matter.\textsuperscript{11} Relapsed encephalitis with acute onset of fever, headache, seizures and focal neurological signs occurring months to years after recovery from the initial acute encephalitis is another characteristic feature of Nipah encephalitis seen in about 10% of the Malaysian patients during follow-up.\textsuperscript{6,2} Although there was report of delayed onset neurological abnormalities seen in 4 out of 22 patients in a follow up study in Bangladesh, manifesting in oculomotor palsy (3) and cervical dystonia (1), none reported fever, seizures, headache during onset of the new neurological deficit as in the Malaysian patients.\textsuperscript{33} All these differences in clinical manifestations probably reflect differences in underlying pathology process due to a genetic variation of the virus.

In summary, there are significant differences in the epidemiologic and clinical features of Nipah virus infection in the Malaysian and the subsequent Bangladesh and Indian outbreaks. Some of these differences are likely to be due to local socio-cultural and economic factors – such as the consumption of date palm juice which led to introduction of virus from bats to humans in Bangladesh, and the large commercial pig farming industry, which caused explosive large outbreak from pig-to-pig and pig-to-humans in Malaysia. The differences in mortality are likely to reflect different health care practices and availability of resources. There remain, however, significant differences in epidemiologic and clinical manifestations, which are likely to reflect variation in viral genome. These are the predominance of respiratory involvement, and the importance of human-to-human spread in the Bangladesh and Indian outbreaks. The elucidation of the function of the various viral proteins and the host immune response in different organ systems is likely to shed further light on our understanding of this important disease. There has been report of genetic variation of Nipah virus even within Malaysia.\textsuperscript{34} Clinicians in Asia should continue to be alert to the possibility of Nipah virus infection, and be open to variations in the epidemiologic features and clinical manifestations of Nipah virus infection.

\textbf{REFERENCES}