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NIPAH VIRUS – AN EMERGING LIFE-THREATENING DISEASES – A REVIEW ARTICLE

Medicine

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ABSTRACT

Nipah Virus Infection (NiV) is an emerging infectious disease of public health importance in the South-East Asia Region. It is a zoonotic disease, natural host being fruit bat and intermediate host as pigs. Presents with fever, signs of pneumonia, headache and other neurological symptoms. Disease transmitted by eating fruits bitten by infected animals. Various diagnostic methods are incorporated to diagnosis the disease. Medical treatment though ineffective but prognosis improves with timely management. Vaccine for the virus is still under development.

KEYWORDS

Introduction

Nipah Virus Infection (NiV) is an emerging infectious disease of public health importance in the South-East Asia Region. The virus is named after the Malaysian village Sungai Nipah, where it was first discovered.[1] NiV has infected 477 people and killed 252 since 1998. Case fatality rate of NiV ranges from 40-70% although it has been as high as 100% in some outbreaks. Infected bats shed virus in their excretion and secretion such as saliva, urine, semen and excreta but they are symptomless carriers. Procedures for the laboratory diagnosis of NiV include serology, histopathology, PCR and virus isolation. Serum Neutralization Test, ELISA, RT-PCR are used for laboratory confirmation. There is no effective treatment for Nipah virus disease, but ribavarin may alleviate the symptoms of nausea, vomiting, and convulsions.[21] Treatment is mostly focused on managing fever and the neurological symptoms.

History

The virus is named after the Malaysian village Sungai Nipah, where it was first discovered.[1] This virus along with Hendra virus comprises a new genus designated Henipavirus in the subfamily Paramyxovirinae.[2] First appeared in domestic pigs in Malaysia and Singapore in 1998 and 1999.

There is evidence of Nipah infection among several species of domestic animals including dogs, cats, goats, and horses. Sheep may also be affected. However, since the initial outbreak it has primarily affected humans in different parts of the world.

Epidemiology

So far, NiV has infected 477 people and killed 252 since 1998. The distribution of NiV outbreaks in Bangladesh and India during 2001 to 2008. Outbreaks of Nipah in south Asia have a strong seasonal pattern and a limited geographical range. The morbidity and mortality data of human NiV infection is presented in Table 1. Case fatality rate of NiV ranges from 40-70% although it has been as high as 100% in some outbreaks. The presence of Nipah virus antibodies have indicated that dogs, cats, goats and horses were infected, but only if exposed to infected pigs in Malaysia.[3] Their role in transmitting infection to humans was not determined.

NiV outbreaks in India

The first outbreak of NiV in Siliguri, eastern India, triggered a big scare among the public because of the clustering of deaths in space and time. Cases and deaths among doctors and health-care providers, and rumours of it being pneumonic plague or some unknown disease with no clue to diagnosis and treatment resulted in a panic situation with scores of people fleeing the town. Person-to-person transmission, including nosocomial transmission, which was not reported in earlier NiV outbreaks in Malaysia and Singapore, was apparent in the Siliguri outbreak. For this reason, NiV was not considered in the differential diagnosis. The lesson learnt is that in an outbreak of unknown aetiology, we need to be careful before we exclude newer pathogens as possible aetiological agents. Also, laboratory confirmation may not be forthcoming early in such outbreaks. Therefore, there is an urgent need to strengthen epidemiological investigation capabilities so that possible mode(s) of transmission and the reservoir of infection can be identified and appropriate control measures instituted in a timely manner. The Siliguri outbreak highlighted the importance and urgency of establishing a strong surveillance system supported by a network of state-of-the-art laboratories.

Year/Month	Location	No. cases	No. deaths	Case Fatality
Sep 1998 - Apr 99	Malaysia (Perak, Selangor and Negeri Sembilan states)	265	105	40%
Mar 1999	Singapore	11	1	9%
Feb 2001	Siliguri (India)	66	45	68%
Apr-May 2001	Meherpur, Bangladesh	13	9	69%
Jan 2003	Naogaon, Bangladesh	12	8	67%
Jan-Apr 2004	Goalando, Bangladesh Faridpur, Bangladesh	29 36	22 27	76% 75%
Jan-Mar 2005	Tangail, Bangladesh	12	11	92%
Jan-Feb 2007 Mar-Apr 2007 April 2007	Thakurgaon, Bangladesh Kushtia, Bangladesh Nadia, India	7 8 5	3 5 5	43% 63% 100%
Feb 2008 Apr 2008	Manikgonj and Rajbari, Shatkira and Jessore	11 2	6 1	55% 50%
Total		**477**	**248**	52%

Table 1: Morbidity and mortality due to Nipah or Nipah-like virus, Asia-Pacific Region, 1998-2008.

The mode of transmission

Infected bats shed virus in their excretion and secretion such as saliva, urine, semen and excreta but they are symptomless carriers. The NiV is highly contagious among pigs, spread by coughing. Direct contact with infected pigs was identified as the predominant mode of transmission in humans when it was first recognized in a large outbreak in Malaysia in 1999.[4] Ninety percent of the infected people in the 1998-1999 outbreaks were pig farmers or had contact with pigs. There is strong evidence that emergence of bat-related viral infection communicable to humans and animals has been attributed to the loss of natural habitats of bats. As the flying fox habitat is destroyed by human activity the bats get stressed and hungry, their immune system gets weaker, their virus load goes up and a lot of virus spills out in their urine and saliva. Similar fluctuation of virus shedding may be associated with the stressful physiological conditions or seasons. Evidence of seasonal preference of transmission in P.lylei was recently demonstrated in a study in Thailand. The period April-June was the

time (highest in May) when viral RNA could be mainly detected in urine which was associated with a fluctuation of population numbers that was observed only in May and correlated with young bats leaving to fly.

There were focal outbreaks of NiV in Bangladesh and India in 2001 during winter. Drinking of fresh date palm sap, possibly contaminated by fruit bats (P. giganteus) during the winter season, may have been responsible for indirect transmission of Nipah virus to humans.[5]

There is circumstantial evidence of human-to-human transmission in India in 2001. During the outbreak in Siliguri, 33 health workers and hospital visitors became ill after exposure to patients hospitalized with Nipah virus illness, suggesting nosocomial infection.[6]

During the Bangladesh outbreak the virus is suggested to have been transmitted either directly or indirectly from infected bats to humans. Strong evidence indicative of human- to-human transmission of NiV was found in Bangladesh in 2004.[7]

Objectives

The main objective of NiV disease surveillance is to rapidly detect and potentially forecast epidemic activity. The objectives of surveillance that are most applicable to NiV infection include:

- detection of outbreaks quickly for control interventions;
- monitoring trends in the distribution and spread of the disease, over time and geographically; facilitating planning and resource allocation on the basis of lessons learnt from interventions and their impact;
- evaluation of the effectiveness of prevention and control measures.

Risk of Exposure

In the Malaysia and Singapore outbreak, Nipah virus infection was associated with close contact with Nipah virus-infected pigs. In Bangladesh and India, exposure has been linked to consumption of raw date palm sap or coconut/palm tree sap contaminated with bat excrement, or climbing trees coated in bat excrement, or contact with bats. It is also attributed to eating of fruits contaminated by bat secretions. Importantly, human-to-human transmission has been documented and exposure to other Nipah virus infected individuals is also a risk factor.

Clinical presentation

In animals, typical clinical symptoms are observed in pigs where respiratory symptoms dominate. Nipah virus disease in pigs is also known as porcine respiratory and neurologic syndrome as well as barking pig syndrome based on clinical observation.

Symptoms of NiV infection in humans are similar to that of influenza such as fever and muscle pain. In some cases, inflammation of the brain occurs leading to disorientation or coma. Encephalitis may present as acute or late onset. The latter may be difficult to diagnose since exposure may have taken place several months earlier. Further, those who may have recovered from an acute episode may also have a relapse. Nevertheless, magnetic resonance of the brain is helpful in differentiating Nipah encephalitis from other encephalitis as well as in defining between acute and late onset or a relapsed form of the disease. The case fatality rate ranges from 9 to 75%. Some patients have a respiratory illness during the early part of their infections, and half of the patients showing severe neurological signs showed also pulmonary signs. Long-term sequelae following Nipah virus infection have been noted, including persistent convulsions and personality changes. Latent infections with subsequent reactivation of Nipah virus and death have also been reported months and even years after exposure.
Incubation period: 4 to 18 days.

Standard case definitions

The cases are defined for clinical case identification or for surveillance activities. The suggested standard case definitions for Nipah cases are as follows:

1. Suspected (clinical) Nipah case: Patient with an epidemiological link or from a community affected by an outbreak who has:

i) fever with acute onset of altered mental status or seizure and/or
ii) fever with headache and/or
iii) fever with acute onset of cough with shortness of breath.

2. Probable Nipah case: Suspect cases, and/or who died before complete diagnostic specimens could be collected, including a serum antibody test 14 days after onset of illness.
3. Confirmed Nipah case: Suspected/probable case having, in addition, laboratory

confirmation of NiV infection either by:

i) IgM antibody against NiV identified in serum or CSF, or
ii) NiV RNA identified by RT-PCR from respiratory secretions, urine or cerebrospinal fluid, or
iii) isolation of NiV from respiratory secretions, urine or cerebrospinal fluid or other tissue specimens.

Laboratory diagnosis

Procedures for the laboratory diagnosis of NiV include serology, histopathology, PCR and virus isolation. Serum Neutralization Test, ELISA, RT-PCR are used for laboratory confirmation.

Most countries in the South-East Asia Region do not have adequate facilities for diagnosing the virus or on ways of controlling it. Bangladesh, India and Thailand have developed laboratory capacity for diagnostic and research purposes.

Nipah virus is classified internationally as a biosecurity level (BSL) 4 agent. BSL 2 facilities are sufficient if the virus can be first inactivated during specimen collection.[8] There are a few laboratories in which the virus can be studied safely without a risk of it "escaping" and infecting more people.

Virus isolation

Ideally, virus isolation should be attempted to confirm any new NiV outbreak. However, NiV being a BSL-4 level agent, biosafety considerations require a BSL-4 laboratory facility.[9]

NiV can be grown in a range of cultured cells in the laboratory. It grows well in Vero cells, with development of characteristic syncytia with the nuclei arranged around the periphery of the multinucleated cell. Identification of virus isolates may be done by immune staining of fixed, infected cells, neutralization with specific antisera, RT-PCR of culture supernatants and electron microscopy. Isolation of NiV from the CSF has been strongly associated with mortality.[10]

Histopathology and immunohistochemistry

Immunohistochemistry is highly recommended for initial NiV virus diagnosis. It is one of the safest tests as it is performed on formalin-fixed tissues. Since the primary pathology occurs in the vascular endothelium, viral antigen can be detected in a range of tissues. The sensitivity and specificity is not very high, but sensitivity can be improved by sampling an adequate number of animals at necropsy, perhaps over a period of a few days if the disease is progressing on a farm. Also, an adequate range of tissues should be sampled.[10,11,12]

Serology

Indirect ELISA may be used for detecting IgG and capture ELISA for IgM antibodies against NiV, and can be conducted from inactivated serum in BSL-2 facilities. The IgG ELISA test is used for serosurveillance in humans, swine, bats and peridomestic and domestic animals. Since NiV is closely related to Hendra virus, ELISAs using Hendra virus or NiV antigen may cross-react and could be used detect antibodies to both viruses.[13,14,15,16]

RT-PCR

There is a range of PCR techniques described to detect RNA from NiV including conventional RT-PCR, nested conventional RT-PCR, and real-time RT-PCR. Detection of viral RNA and its quantitation using real-time RT-PCR can be done in serum, CSF, throat swabs, urine and viral cultures from the CSF, throat swabs or tissues.[12,9]

RT-PCR is the most practical test in countries where either BSL-4 laboratory or ELISA reagents are not available. BSL-2 facilities are sufficient for conducting molecular tests if the samples can be first inactivated during specimen collection. RT-PCRs can be used for detection of viral sequences in fixed or fresh tissue or CSF specimens.[14,17,18,19]

Electron microscopy

Negative contrast electron microscopy and immuno-electron microscopy of culture media provides information on structure and antigenic activity of viruses in cell culture.[12,20,9]

Prevention and control

There is no effective treatment for Nipah virus disease, but ribavarin may alleviate the symptoms of nausea, vomiting, and convulsions.[21] Treatment is mostly focused on managing fever and the neurological symptoms. Severely ill individuals need to be hospitalized and may require the use of a ventilator.

Human-to-human transmission of NiV has been reported in recent outbreaks demonstrating a risk of transmission of the virus from infected patients to healthcare workers through contact with infected secretions, excretions, blood or tissues. Healthcare workers caring for patients with suspected or confirmed NiV should implement Standard Precautions when caring for patients and handling specimens from them.

A vaccine is being developed. A recombinant sub-unit vaccine formulation protects against lethal Nipah virus challenge in cats.[21] ALVAC Canarypox vectored Nipah F and G vaccine appears to be a promising vaccine for swine and has potential as a vaccine for humans.[22]

The main strategy is to prevent NiV in humans. Establishing appropriate surveillance systems will be necessary so that NiV outbreaks can be detected quickly and appropriate control measures initiated.

References

1. Anno. (1999). Outbreak of Hendra-like virus – Malaysia and Singapore, 1998-99. Morb. Mort. Weekly Rep., 48 (13), 265-269.
2. International Committee on Taxonomy of Viruses [database on the Internet]. [cited 2004 Dec 1]. Available from http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/index.htm
3. Mohd Nor MN, Gan CH, Ong BL. Nipah virus infection of pigs in peninsular Malaysia. Rev. Sci. Tech. Off. Int. Epiz. 2000;19:160-65.
4. Goh KJ, Tan CT, Chew NK, Tan PSK, Kamarulzaman A, Sarji SA, Wong KT, Abdullah BJJ, Chua KB, Lam SK. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. N. Engl. J. Med. 2000;342, 1229–1235.
5. Luby, SP, Rahman, M, Hossain, MJ, Blum, LS, et al. Foodborne transmission of Nipah virus, Bangladesh. Emerg Infect Dis 2006; 12:1888-1894.
6. Chadha MS, Comer JA, Lowe L, Rota PA, Rollin PE, Bellini WJ, et al. Nipah virus-associated encephalitis outbreak, Siliguri, India. Emerg Infect Dis. 2006;12:235-40.
7. Gurley E, Montgomery JM, Hossain MJ, Bell M, Azad AK, Islam MR, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. Emerg Infect Dis. 2007;13:1031-7.
8. Daniels, P., Ksiazek, TG, Eaton, BT. Laboratory diagnosis of Nipah virus and Hendra infections. Microbes Infect., 3. 2001:289-295.
9. Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah Virus. Clin Infect Dis. 2009;49:1743–48.
10. Daniels P, Ksiazek TG, Eaton BT. Laboratory diagnosis of Nipah virus and Hendra infections. Microbes Infect. 2001;3:289–95.
11. Harcourt BH, Tamin A, Ksiazek TG, Rollin PE, Anderson LJ, Bellini WJ, et al. Molecular characterization of Nipah virus, a newly emergent paramyxovirus. Virology. 2000;271:334-349.
12. Food and Agriculture Organization of the United Nations Regional Office for Asia and the Pacific and Animal Production and Health Commission for Asia and the Pacific (APHCA). Manual on the diagnosis of Nipah virus infection in animals RAP publication no.2002/01. January 2002 http:// www. fao. org/ docrep/ 005/ ac449e/ ac449e07. htm#bm07 - accessed 4 April 2016.
13. Chua KB, Bellini WJ, Rota PA, Harcourt BH, Tamin A, Lam SK, et al. Nipah virus: a recently emergent deadly paramyxovirus. Science. 2000;288:1432–5.
14. Field H, Young P, Yob JM, Mills J, Hall L, Mackenzie J. The natural history of Hendra and Nipah viruses. Microbes Infect. 2001;3:307–14.
15. Daniels P, Ong B, Jamaluddin A. Nipah virus diagnosis and control in swine herds. In: Trends in Emerging Viral Infections of Swine. Ames: Iowa State Press; 2001.
16. Kaku Y, Noguchi A, Marsh GA, McEachern JA, Okutani A, Hotta K, et al. A neutralization test for specific detection of Nipah virus antibodies using pseudotyped vesicular stomatitis virus expressing green fluorescent protein. J Virol Methods. 2009;160:7–13.
17. Hooper P, Zaki S, Daniels P, Middleton D. Comparative pathology of the diseases caused by Hendra and Nipah viruses. Microbes Infect. 2001; 3:315–22.
18. Wacharapluesadee S, Hemachudha T. Duplex nested RT-PCR for detection of Nipah virus RNA from urine specimens of bats. J Virol Methods. 2007;141:97– 101.
19. Bossart KN, Bingham J, Middleton D. Targeted strategies for henipavirus therapeutics. Open Virol J. 2007;1:14–25.
20. Thorner AR, Dolin R. Zoonotic paramyxoviruses: nipah, hendra, and menangle viruses. In: Bennett JE, Dolin R, Blaser M, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th edition. Elsevier, 2014:1974–80.
21. Chong HT, Kamarulzaman A, Tan CT, Goh KJ, Thayaparan T, Kunjapan SR, et al. Treatment of acute Nipah encephalitis with ribavirin. Ann Neurol. 2001;49:810-3.
22. McEachern JA, Bingham J, Crameri G, Green DJ, Hancock TJ, Middleton D, et al. A recombinant subunit vaccine formulation protects against lethal Nipah virus challenge in cats. Vaccine. Volume 26, Issue 31, 23 July 2008:3842-3852.