UPDATE ARTICLE

Nipah Virus Infection

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Abstract

Nipah Virus Infection is an emerging zoonotic infection which presents with acute encephalitis and respiratory distress syndrome. It is associated with high mortality and classified as Biosafety level 4 organisms in view of its features which make it a potential agent for Bioterrorism. Experience with broad spectrum antiviral agent Ribavirin is promising in reducing the mortality and morbidity

Introduction

Nipah virus infection is an emerging zoonotic disease associated with high mortality rate in human being which varies from 40% to 100%. It presents with predominant respiratory and neurologic features. Recently there was an outbreak in Perambra, Calicut district of Kerala, India. In this article we review common clinical features of Nipah virus infection and its management aspects.

Epidemiology

The first human outbreak of Nipah virus was reported from Malaysia among pig farmers in 1998 which was associated with 40% case fatality rate. The virus was named nipah after the name of the village of "Sungai Nipah", in Malaysia, were it was first identified. Singapore outbreak in 1991 was associated with 9% mortality, whereas 2001 outbreak in Siliguri district of West Bengal was associated with 74% mortality. There are several outbreaks in Bangladesh and the first reported outbreak was in 2001 and it has become an epidemic in Bangladesh. Majority of cases are in the northern- central districts of Bangladesh where date palm sap collection is common and the area is referred as "Nipah belt". 2007 outbreak in Nadia district, West Bengal, India was associated with 100% case fatality. Nipah virus Infection, which is fatal zoonotic infection, has got many features that make it a potential agent for Bioterrorism and is classified as Biosafety level 4 organisms.

In the recent outbreak (2018 may) in Perambra, Kerala, India patients developed both neurological and respiratory symptoms and there was high human to human transmission. Most appreciable fact about the Kerala outbreak was that the team of doctors were able to identify the nipah virus infection in the second patient itself, compared to other outbreaks where it took months to identify causative organism. Early diagnosis of nipah outbreak helped to effectively implement preventive measures.

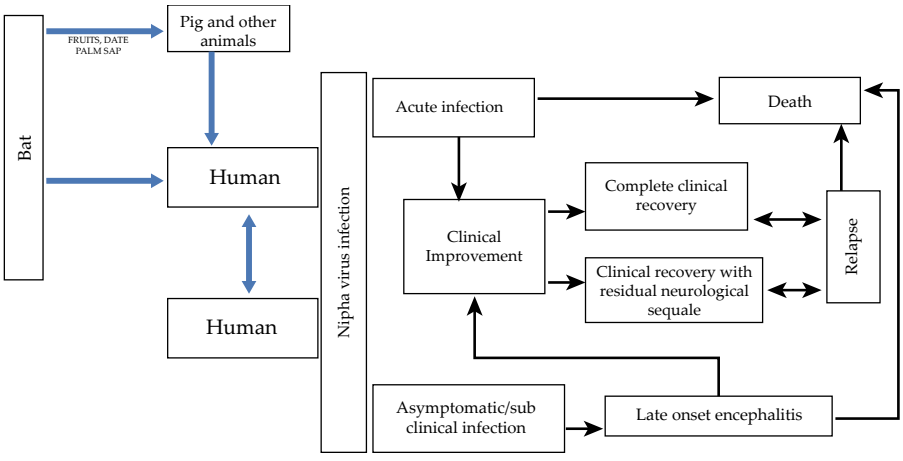

Fig. 1: Nipah infection: overview

Nipah Virus

Nipah virus belongs to henipavirus genius of paramyxovirus family and closely related to Hendra virus and Cedar virus. The virus in an envelope virus having negative sense single stranded non segmented RNA genome. It is inactivated by 60^0c for 60 minutes. It is susceptible to common soaps, disinfectants and lipid solvents like alcohol, ether and sodium.

Natural host

Fruit bats of Pteropus genus, Pteropodidae family are the natural host for Nipah virus and they are migratory. The bats carrying virus are asymptomatic. Recently African fruit bats which belong to family pteropodidae, genus Eidolon is also found positive for Nipah virus. It is hypothesized that geographic distribution of henipavirus overlaps with that of pteropus bats.

Nipah outbreak in pigs and other domestic animals like horse, goats, sheep, cat and dogs were first described during the Malaysian outbreak in 1999. Pigs can be asymptomatic or symptomatic with neurological and respiratory involvement. Pigs are infective during incubation period which varies from 4 days to 14 days.[1]

Human infection

Human infection occurs on exposure

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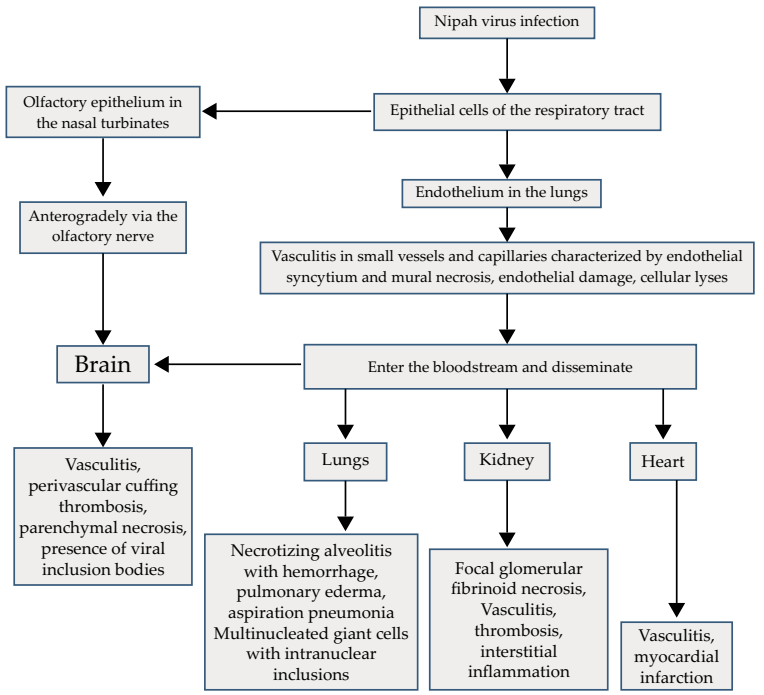

Fig. 2: Nipah infection: Pathophysiology

to infected domestic animals like pig, cow or by consumption of fresh date palm soup contaminated with infected bat saliva, urine or fecal matters. Person to person transmission by droplet infection is also common during the outbreak. Exposure to patients' secretion is a risk factor for the development of disease. Incubation period varies from 4 days to 45 days. In person to person transmission the median incubation period is 6-11 days.[2]

Transmission

In Malaysian outbreak, it transmitted from natural host (fruit bat) to amplification host (pigs) and then to human being, by direct contact with sick pigs or their contaminated tissue. Transmission occurred via respiratory droplet, contact with body secretions or tissues of sick animals (Figure 1). But in Bangladesh outbreak people were directly infected from fruit bats without transmission into the amplifying host. Consumption of fruits, fruit products and raw date palm sap contaminated with urine or saliva of infected bats resulted in the outbreak in Bangladesh. People working in the trees also got infected.[3] Virus spread directly from person to person through close contact, especially with the patients secretions. In Siliguri, India outbreak, 75% of cases were among the hospital staff or visitors indicating the high risk of transmission via close contact.

Pathology

Nipah virus infection leads to marked vasculitis and endothelial damage and cellular lyses in arterioles, venules and capillaries of various organs. HNV productively infects monocyte, CD6+CD8+ T lymphocyte and NK cells.[4] CD6 which is a ligand for activated Leukocyte Cell Adhesion Molecule, ALCAM (CD166) is highly expressed in microvascular endothelial cells of lungs and brain resulting in preferential tropism. Vasculitis and cellular damage in organs like brain, lungs and kidney produce various clinical features (Figure 2).

Clinical Features

Nipah virus infected individual usually presents with high fever, headache, myalgia and sore throat. The respiratory and neurological features start by about 4 days after the onset of fever. The neurological features include dizziness, vomiting, impairment in spatial perception, myoclonus, altered consciousness, drowsiness, seizure and abnormal plantar response which rapidly progressed to comma within 24-48 hours suggestive of acute encephalitis. Signs of brain stem dysfuction like hypertension and tachycardia were also present. Patients developed respiratory symptoms like cough, breathlessness and features of atypical pneumonia and acute respiratory distress. Seriously affected patients develop septicemia, renal impairment and gastro-intestinal bleeding. In Malaysian outbreak it was predominantly neurological features (encephalitis presentation) where as in Bangladesh, both respiratory and neurological features were common. This may explain the high risk of human to human transmission observed in Bangladesh outbreak. The difference in the clinical presentation may be due to genetic difference in the nipah virus strain. The outbreak in Malaysia was associated with single strain, where as in Bangladesh it is due to diverse strain.[5] Case fatality rate varies from 40-100% in different outbreaks. In patients with Nipah virus infection high fever, respiratory symptoms and absence of plantar reflex is associated with high risk of mortality. About 20% of survivors were having residual neurological consequence like persistent convulsions and personality changes.[1] Recovered patient may experience relapse years later and sub clinically infected individual may develop neurological features years later[6] (Figure 1).

Laboratory Findings

Routine blood examination may show leucopenia and thrombocytopenia. Liver enzymes may be elevated. Patients with respiratory symptoms may show features suggestive of atypical pneumonia or acute respiratory distress syndrome. In patients with encephalitis CSF examination shows elevated blood cell count and protein. CT brain is normal in most of the cases were as MRI brain shows widespread focal lesions in the sub cortical and deep white matter. But normal CSF does not rule out nipah virus infection in patients with encephalitis.

Virus infection can be diagnosed by different tests like ELISA, PCR assay, serum neutralization, immunofluoresence assay and virus isolation by cell culture. Usually blood, urine, throat scrub and CSF sample are collected for diagnostic testing. From brain, lung, kidney and spleen samples virus isolation can be done using African green monkey kidney (varo) and rabbit kidney (RK-13) cell culture.[7] Serum neutralization (SN) test is the reference standard for anti-Nipah virus antibody detection.[7] Indirect and capture ELISA can be used for detection

of IgG and IgM antibody respectively.

Treatment

There are no specific antiviral drugs effective against Nipah currently. The main treatment is intensive support care for ARDS and encephalitis and treatment of symptoms.

Ribavirin is broad spectrum antiviral agent which is active against both RNA and DNA virus and is tried in patients with Nipah virus infection. It cross blood brain barrier following oral administration making it useful for the treatment of viral encephalitis. Initial trial in Malaysia with ribavirin showed 36% reduction in mortality and increased survival without neurological deficits. Ribavirin also reduces the duration of ventilator support and total hospital stay in patients with nipah virus infection.[8]

Neutralizing human mechanical antibody the m102.4, that recognize the receptor binding domain of the nipah virus G glycoprotein is successfully tested in animal model.[9]

Favipiravir (T-705; 6-flouro-3-hydroxy-2- pyrazinecarboxamine) a purine analogue that inhibit viral RNA-dependent RNA polymerase (RdRp), which has got potent anti-influenza activity also act against various RNA viruses including bunyaviruses, arenaviruses, filoviruses, norovirus, flaviviruses, alphaviruses, enteroviruses, paramyxoviruses, Ebola virus and rhabdoviruses. Various trails with Favipiravir shows promising results in nipah virus infection.[10]

Adenosine nucleoside analogue GS-441524, its monophosphate prodrug GS-5734 and another nucleoside analogue, R1479 (balapiravir), was also found to be active against NiV and HeV in various studies.[11,12]

Prevention

No effective vaccine is available currently to prevent Nipah infection. Controlling Nipah virus infection in domestic and farm animals is important to prevent further spread during an outbreak. Improving the public awareness and helping them to avoid exposure to virus is important to control infection. Decreasing bat access to date palm sap and boiling freshly collected date palm juice will help to reduce the risk of bat to human transmission. Fruits should be thoroughly washed and peeled before eating. Avoid close contact with infected individual to reduce the risk of human to human transmission. Those who are taking care of infected individual should use gloves and personal protective equipment (PPE). Regular hand washing should be carried out while caring sick people. Cleaning and disinfection of the environment and equipment along with proper waste management is important in preventing transmission.

Wearing gloves and protective clothing while handling sick animal and their tissue will help to reduce the risk of animal to human transmission. Health care worker caring patients with Nipah Virus infection should implement standard infection control precautions.

Conclusion

Nipah virus is an emerging zoonotic virus which belongs to Paramyxoviridae family. Nipah virus infection presents with neurological and respiratory symptoms and is associated with high mortality. Even though intensive supportive care is the mainstay of treatment, Ribavirin is found to be effective in reducing mortality and delayed neurological sequale. Various infection control precautions will help to control the transmission of infection.

References

1. Wahed F, Kader SA, Akhtarunnessa, Mahamud MM. Nipah Virus: An Emergent Deadly Paramyxovirus Infection in Bangladesh. *J Bangladesh Soc Physiol* 2011; 6:134-139.
2. Hsu VP, Hossain MJ, Parashar UD, Ali MM, Ksiajek TG, Kuzmin I, et al. Nipah Virus Encephalitis Reemergence, Bangladesh. *Emerging Infectious Diseases* 2004; 10:2082-2087.
3. Montgomery JM, Hossain MJ, Gurley E, Carroll GD, Croisier A, et al. Risk factors for Nipah virus encephalitis in Bangladesh. *Emerg Infect Dis* 2008; 14:1526-1532.
4. Stachowiak B, Weingartl HM. Nipah virus infects specific subsets of porcine peripheral blood mononuclear cells. *PLoS One* 2012; 7:e30855.
5. Bellini WJ, Harcourt BH, Bowden N, Rota PA. Nipah virus: an emergent paramyxovirus causing severe encephalitis in humans. *J Neuro- virol* 2005; 11:481–7.
6. Chong HT, Tan CT. Relapsed and late-onset Nipah encephalitis, a report of three cases. *Neurol J Southeast Asia* 2003; 8:109-112.
7. Giangaspero M. Nipah Virus. *Trop Med Surg* 2013; 1:129. doi:10.4172/2329-9088.1000129.
8. Chong HT, Kamarulzaman A, Tan CT, Goh KJ, Thayaparan T, Kunjapan SR, Chew NK, Chua KB, Lam SK. Treatment of acute Nipah virus encephalitis with ribavirin. *Ann Neurol* 2001; 49:810–813.
9. Bossart KN, Zhu Z, Middleton D, Klippel J, Crameri G, et al. A Neutralizing Human Monoclonal Antibody Protects against Lethal Disease in a New Ferret Model of Acute Nipah Virus Infection. *PLoS Pathog* 2009; 5:e1000642.
10. Dawes BE, Kalveram B, Ikegami T, et.al. Favipiravir protects against Nipah virus infection in the hamster model. *Sci Rep* 2018; 8:7604.
11. Lo MK, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep* 2017; 7, 43395, https://doi. org/10.1038/srep43395.
12. Hotard AL, He B, Nichol ST, Spiropoulou CF, Lo MK. 4′-Azidocytidine (R1479) inhibits henipaviruses and other paramyxoviruses with high potency. *Antiviral Res* 2017; 144:147–152.