Nipah virus (NiV)

Pathogen

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Overview

Transfusion-transmission of NiV has not been reported but it is considered theoretically possible as it has been detected at low levels in blood samples. Although it is classified as a catastrophic severity agent with a high mortality rate it is a low risk to blood safety as NiV does not occur in Australia, outbreaks elsewhere are rare and there are donation restrictions for donors who return from outbreak areas overseas.

Classification and morphology

NiV belongs to the *Paramyxoviridae* family, *Orthoparamyxovirinae* subfamily and *Henipavirus* genus and is closely related to Hendra virus (HeV). The two viruses share antigenic similarities and amino acid sequence homology that varies between 71% and 92% across the different regions of the genome. Similar to HeV, NiV has a single-stranded, negative-sense RNA genome of approximately 18,000 nucleotides which is unusually large within the *Paramyxoviridae* family; the enveloped viral particles range in size from 120−500 nm.

Molecular analysis of NiV isolates from Malaysia, Cambodia, India and Bangladesh has indicated that there are two main clades representing two separate introductions into South East Asia (mean estimated dates being 1985 and 1995, respectively) and several strains of the virus. NiV was first isolated from the infected cerebrospinal fluid of a patient in the village of Sungai Nipah in Malaysia during a viral encephalitis outbreak in 1998-1999.

[1–5]

Associated disease

The incubation period for NiV appears to vary between strains. In the Malaysian outbreak (1998-99) the incubation period ranged from four days to two months, but most cases (90%) had an incubation period of less than two weeks. In the subsequent outbreaks in Bangladesh and India, the incubation period was 6–11 days.

NiV infections can vary from asymptomatic to fatal encephalitis. NiV causes multi-organ vasculitis with a predilection for the CNS. Microvascular endothelial cell damage predominantly underlies the pathological changes in NiV infections. During the index Malaysian outbreak infected subjects initially developed influenza-like symptoms of fever, headaches, myalgia, vomiting and sore throat. This was often followed by dizziness, drowsiness, altered consciousness, segmental myoclonus, tachycardia, areflexia and hypotonia. About 14% of patients developed severe respiratory symptoms. The incubation period in humans ranged from four days to two months with 90% at two weeks or less. The rate of subclinical infection ranged from 8−15%. The mortality rate was approximately 40%, with a mean duration of 16 days from onset of symptoms to death.

However, there appears to be differences in pathogenicity and disease symptoms between different strains of NiV. In contrast to the Malaysian outbreak, during the subsequent outbreaks in Bangladesh and India, the disease incubation period was substantially shorter (6–11 days), approximately 70% of subjects reported

respiratory distress and approximately 90% of cases in the 2001 and 2004 Bangladeshi outbreaks had altered mental status compared with 21% in the Malaysian outbreak. Additionally, the case fatality rates were generally higher in the Bangladeshi outbreaks (70–100%).

Most people who survive acute encephalitis make a full recovery but around 20% are left with residual neurological consequences. A small number of people who recover subsequently relapse while some who have asymptomatic or non-encephalitic infections will subsequently develop late-onset encephalitis.

[6–10]

Blood phase

The blood phase of NiV infection in humans has not been well characterised but it appears that acute infection is accompanied by a short low level viraemia. NiV RNA is rarely detected in human blood samples and, when detected, it is at low levels.

Similar findings have also been reported for samples from pigs and cats. A presymptomatic viraemic period has not been defined but cannot be excluded. During the late stages of disease, virus replication spreads from the respiratory epithelium to the endothelium in the lungs. The infection can sometimes trigger a prominent vasculitis in small vessels and capillaries and NiV can then enter the bloodstream and disseminate throughout the host in either free form or by binding to host leucocytes.

The serological response to NiV infection involves both IgM and IgG production. The kinetics of IgM and IgG seroconversion in NiV infection has been reported in a study of Malaysian patients admitted to hospital between 1998 and June 1999. IgM was detectable in 50% of patients by day one of symptom onset, 71% by day four and 100% by day nine. IgM remained detectable for a mean of 83 days with the longest period being 228 days. The detection rate for IgG varied between 10% and 31% in the first 10 days after symptom onset and was 100% by day 18.

[4,7–9,11]

Chronic carriage

NiV can apparently establish persistent infection in (at least) a small proportion of infected individuals as indicated by relapsing and late-onset encephalitis. Relapsing encephalitis has been reported to occur from several months to several years after acute infection, with the longest reported period being 11 years. Late or delayed onset encephalitis has been reported from several months to a few years following acute infection. Additionally, neurologic dysfunction following acute infection may continue for several years after acute infection.

[7,11–17]

Human exposure routes

During the initial outbreaks in Malaysia and Singapore most human infections resulted from direct contact with infected pigs. Transmission is thought to have occurred via respiratory droplets (as NiV is shed in respiratory secretions) or through contact with infected animal tissue or urine. During subsequent outbreaks in Bangladesh and India exposure was predominantly due to consumption of date palm sap or its fermented product that had been contaminated with urine or saliva from infected fruit bats, or human-to-human via direct

contact with infectious secretions (such as saliva, urine, vomitus or diarrhoea) of patients with clinical disease.

[3,7,18–21]

Vector and reservoir

The natural reservoir hosts for NiV are fruit bats (known as flying foxes) of the *Pteropodidae* family, particularly the *Pteropus* genus. Species in which neutralising antibodies to NiV have been detected include *P. hypomenalus*, *P. vampyrus* and *P. giganteus*. NiV-infected bats develop subclinical infection with intermittent viral secretion via the urine. Unique strains of the virus circulate in different areas indicating that they have co-evolved with local natural reservoirs. The use of urine during mutual grooming by fruit bats is thought to sustain intermittent transmission throughout bat roosts.

Pigs are amplifying hosts for NiV. During the initial Malaysian outbreak in 1998-99 pigs were probably infected with NiV by eating fruit contaminated with bat secretions with subsequent pig-to-pig transmission via oronasal secretions.

In addition, serological studies indicate that a number of mammalian species can be secondarily infected with NiV including dogs, cats, ferrets, goats and horses all of which appear to be dead-end hosts.

[3,6,18,19,22,23]

At risk populations

Individuals at risk of NiV infection include those who consume date-palm sap or its fermented product in areas with infected fruit bats or have contact with infected bats, those in contact with infected pigs during outbreaks (particularly where there are large numbers of pigs in close quarters) and those in close physical contact with infected people including health-care settings.

[18,19,21]

Transfusion-transmissibility

There have been no reported cases of transfusion-transmitted NiV. However, as NiV infection appears to include a viraemic phase (albeit brief and low level), transfusion-transmission cannot be excluded but would appear to represent a low risk. There is the possibility of a viraemic phase in late infection by which time infected individuals would be symptomatic.

[4, 7-9]

Treatment and efficacy

There is no effective treatment for NiV infection. There is some evidence from the initial Malaysian outbreak that ribavirin treatment resulted in a reduced mortality rate in the treated group. In addition, results based on the hamster model of NiV infection have shown that ribavirin was moderately effective at increasing survival time. A number of *in vitro* studies have reported potential antiviral agents for the treatment of human henipavirus infections including gentian violet, brilliant green, gliotoxin and chloroquine.

There is no human vaccine for NiV. However, it is hoped that the development of an equine vaccine against HeV, which is also effective against NiV, will provide viable approaches to develop a human vaccine against both HeV and NiV. In addition, a vaccine has been developed based on recombinant

vesicular stomatitis viruses (rVSV) expressing NiV glycoproteins which has been demonstrated to produce a strong humoral immune response in vaccinated hamsters. The rVSV vectors expressing Nipah virus G or F glycoproteins are prime candidates for new 'emergency vaccines' to be utilized for NiV outbreak management.

[17, 18, 24–29]

Assay and algorithm options for screening and confirmatory / diagnostic testing

There are no TGA- or FDA-approved assays for blood donor screening for NiV.

There are a number of different testing methodologies available for the detection of NiV or exposure to NiV including viral isolation, immunohistochemical techniques, electron microscopy, polymerase chain reaction (PCR), serum neutralisation test (SNT), enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA) and microparticle immunoassay (MIA). Viral antigen capture ELISAs could provide a high throughput format at relatively low cost for testing large numbers of samples and serve as an alternative to polymerase chain reaction (PCR) assays for rapid detection of NiV. ELISAs are the most common serological assays for detection of antibodies to NiV and ELISAs using recombinant NiV antigens have been developed.

PCR using throat and nasal swabs, cerebrospinal fluid, urine, and blood is recommended for diagnosis in the acute phase. Antibody detection by ELISA for IgG and IgM may be useful a few days after the onset of symptoms, although this test is not currently available in Australia.

[17, 19]

Lifeblood risk assessment for blood components

The first reported outbreak of NiV occurred simultaneously in pigs and humans in Malaysia in 1998-1999. A total of 265 human cases were reported with 105 deaths. During the initial Malaysian outbreak there was spread to Indonesia via two farm workers returning home from working on Malaysian pig farms, and to Singapore where 11 abattoir workers were infected by handling infected pigs from Malaysia.

The disease was eradicated from Malaysia in 1999 by the mass slaughter of pigs. Since 2001, human NiV outbreaks have been reported almost every year in Bangladesh and occasionally in India (2001 and 2007). The case numbers reported for these outbreaks in India and Bangladesh varied from a single case up to 66 cases. For outbreaks with >10 reported cases, the case fatality rate varied between 67% and 92%. In addition, NiV or NiV antibodies have been detected in Cambodia, Thailand, Indonesia, Madagascar and Ghana.

In 2014, an outbreak of neurological and severe influenza-like disease in people was reported in the Philippines following an outbreak of neurological disease and sudden death in horses. Serological evidence and limited viral genome sequencing data from human cases were consistent with NiV, or a very closely related virus, being the causative agent of disease. However, further investigation is required for full characterisation of this virus.

NiV has not been reported in Australia or east of Wallace's line which runs through Indonesia, between Borneo and Sulawesi (Celebes), and

through the Lombok Strait between Bali and Lombok. This has led to the suggestion that Wallace's line is a barrier to NiV. In addition, modelling has indicated that the risk of NiV becoming established in flying foxes in Australia appears to be low. However, it has also been noted that NiV may have pandemic potential as indicated by: (i) susceptible human populations, (ii) a number of strains are capable of limited person-to-person transmission, and (iii) as an RNA virus it has an exceptionally high rate of mutation and if a human-adapted strain were to infect communities in South Asia, high population densities and global movement of people would rapidly spread the infection.

In summary, NiV represents a low risk to blood safety in Australia.

[19,21,30-34]

Current Lifeblood risk management strategy for blood components

Donor deferrals exist for allogeneic/therapeutic donors with current or recurrent infection, past infection and contacts with infectious disease. Lifeblood has donation restrictions after overseas travel for malaria-endemic countries which include NiV-risk countries. These deferrals are regularly reviewed and any outbreaks or new developments are constantly monitored.

Proposed strategy should local outbreak occur

In the unlikely event of a significant local outbreak of NiV, Lifeblood may perform a risk assessment to determine whether additional risk mitigation measures were required. Potential strategies include the implementation of a supplementary question to identify donors visiting/residing in risk areas.

Leucoreduction efficacy

No specific data is available regarding the efficacy of leucoreduction in reducing NiV load in blood donations.

Pathogen reduction efficacy (fresh products)

There is no licensed pathogen reduction technology (PRT) available in Australia, but this could be a future option assuming effective RBC technology is realised. Specific NiV inactivation data has not been reported for the commercially available pathogen reduction technologies.

Pathogen reduction efficacy (plasma derivatives)

All of CSL Behring (CSLB)'s plasma-derived products include specific virus inactivation or virus removal steps designed to ensure viral safety.

[35]

Further information available on the CSL Behring website:

https://www.cslbehring.com/products/safety-and-manufacturing

Disclaimer

Australian Red Cross Lifeblood (Lifeblood) surveillance and Transfusion Related Infectious Diseases (TFIDs) information and documentation (the Documents) have been developed by Lifeblood specifically for our internal use within our operational context.

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