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Review

Nipah virus: An emergent paramyxovirus causing severe encephalitis in humans

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Nipah virus is a recently emergent paramyxovirus that is capable of causing severe disease in both humans and animals. The first outbreak of Nipah virus occurred in Malaysia and Singapore in 1999 and, more recently, outbreaks were detected in Bangladesh. In humans, Nipah virus causes febrile encephalitis with respiratory syndrome that has a high mortality rate. The reservoir for Nipah virus is believed to be fruit bats, and humans are infected by contact with infected bats or by contact with an intermediate animal host such as pigs. Person to person spread of the virus has also been described. Nipah virus retains many of the genetic and biologic properties found in other paramyxoviruses, though it also has several unique characteristics. However, the virologic characteristics that allow the virus to cause severe disease over a broad host range, and the epidemiologic, environmental and virologic features that favor transmission to humans are unknown. This review summarizes what is known about the virology, epidemiology, pathology, diagnosis and control of this novel pathogen. *Journal of NeuroVirology* (2005) **11,** 481–487.

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The viruses in the *Henipavirus* genus of the family *Paramyxoviridae*, Hendra virus (HV) and Nipah virus (NV), emerged during the past decade. HV causes a febrile respiratory illness in humans and animals, and was responsible for the deaths of two humans and 17 horses in three separate incidents in Australia during 1994 to 1999 (Murray *et al*, 1995a, 1995b; Selvey *et al*, 1995). The last known incident of HV infection occurred in Australia during January 1999, but there were no reported human infections (Field *et al*, 2000; Hooper *et al*, 2000).

The first known human infections with NV were detected during an outbreak of severe febrile encephalitis in peninsular Malaysia and Singapore in 1998 to 1999. Direct contact with pigs was the primary source of human infection (CDC, 1999a, 1999b; Chua *et al*, 2000). A total of 276 patients (105 fatal) with viral encephalitis due to NV disease were reported in Malaysia and Singapore, mostly among adult males who were involved in pig farming or pork production activities. More recently, NV has been established as the cause of fatal, febrile encephalitis that occurred in humans in Bangladesh during the winters of 2001, 2003, and 2004 (ICDDRB, 2004a, 2004b; WHO, 2004).

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Virology of the henipaviruses

HV and NV were recently designated as a new genus, *Henipavirus*, within the family *Paramyxoviridae*, subfamily *Paramyxovirinae*. The organization of the genomes of HV and NV suggest that they have a replication strategy that is similar to that of other paramyxoviruses (Figure 1). Though the henipaviruses appear to retain many of the genetic and biologic properties of other members of their subfamily, they also have a number of unique characteristics, which are summarized below. HV and NV share antigenic cross-reactivity with each other, but not with any of the other paramyxoviruses. Phylogenetic analyses place the henipaviruses in a monophyletic group

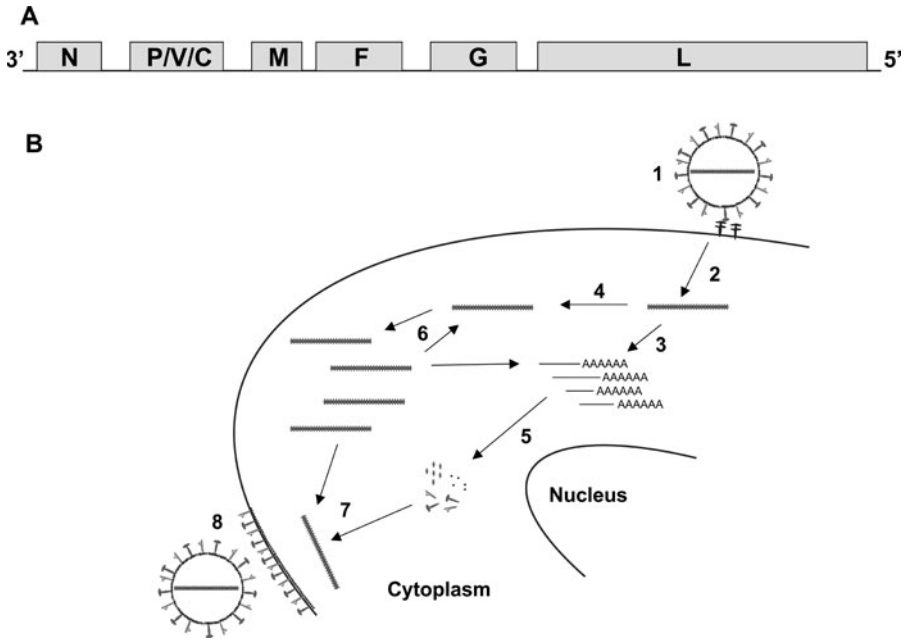

Figure 1 Genomic organization and replication strategy of henipaviruses. Panel **A**, The RNA genomes of henipaviruses are single-stranded and are oriented with negative polarity and a gene order of: 3′ nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), attachment glycoprotein (G), and the RNA-dependent RNA polymerase (L) 5′. Lines depict nontranslated regions and shaded boxes indicate coding regions. Panel **B**, The replication strategy of henipaviruses is predicted to be similar those of other paramyxoviruses. Virion binding to an unidentified cellular receptor(s) is mediated by the G protein, leading to F protein–mediated fusion of the viral envelope with the cellular membrane (1) and release the ribonucleoprotein complex into the cytoplasm (2). The ribonucleoprotein complex composed N, P, and L initiates production of 5′ capped and poly-adenylated viral mRNAs (3), which are translated by cellular ribosomes (5). The F and G proteins are transported to the cell surface. Later in infection, the replication complex (N, P, L) begins to synthesize full-length antigenomic (plus sense) RNA (4), which serves as a template for new genomic RNA. The progeny genomes provide additional templates for mRNA production and replication (6). The viral membrane proteins (G, F, M) and ribonucleoprotein complexes assemble at the plasma membrane (7), where viral budding occurs to release progeny virions (8).

within the *Paramyxovirinae* (Figure 2). One of the more interesting unique biologic features of the henipaviruses is that they have a broad host range both *in vivo* and *in vitro*.

The genomes of HV and NV are 18,234 and 18,246 nucleotides, respectively, making them the largest paramyxovirus genomes reported (Harcourt *et al*, 2001; Wang *et al*, 2000). The increased size is due to a longer open reading frame (ORF) encoding the phosphoprotein (P) and the large nontranslated regions that flank each gene (Harcourt *et al*, 2000, 2001; Wang *et al*, 1998, 2000; Yu *et al*, 1998a, 1998b). The P gene of these viruses encodes three nonstructural proteins (C, V, and W) in addition to P. The C protein is encoded by a second ORF that initiates 23 nucleotides downstream of the translational initiation site for the P ORF (Harcourt *et al*, 2000; Wang *et al*, 1998).

The P genes of both HV and NV contain an RNA editing site that it is identical to the editing site found in measles virus (MV) (Harcourt *et al*, 2000; Wang *et al*, 1998). The addition of a single G allows expression of the V protein, whereas addition of two Gs allows expression of a protein analogous to the W protein of Sendai virus (Delenda *et al*, 1998; Harcourt *et al*, 2000; Steward *et al*, 1993; Vidal *et al*, 1990). The V and W proteins appear to be virulence factors because cells expressing both V and W of NV block activation of an interferon (IFN)-inducible promoter in primate cells (Park *et al*, 2003). The V of NV formed high-molecular-weight complexes with STAT1 and STAT2, which prevented both the activation and nuclear transportation of STAT1 (Rodriguez *et al*, 2002, 2003).

The L proteins of the henipaviruses have the six linear domain structure found within the polymerase proteins of all viruses in the order *Mononegavirales*. A highly conserved GDNQ sequence within domain III that is conserved in most of the *Mononegavirales* viruses is changed to GDNE in the henipaviruses and Tupaia virus (Poch *et al*, 1990; Tidona *et al*, 1999; Harcourt *et al*, 2000; Wang *et al*, 2001).

The cleavage site of the fusion (F) protein of the henipaviruses contains a single basic amino acid and thus does not contain the R-X-R/K-R consensus sequence for furin proteases that is seen in the morbilliviruses, rubulaviruses, and pneumoviruses (Lamb and Kolakofsky, 2000). The cellular protease(s) that cleaves the F of henipaviruses is unidentified though basic amino acids are not required for cleavage (Moll *et al*, 2004). The henipaviruses are unique in that they have a leucine residue at the amino terminus of F_1 instead of the phenylalanine found in most other

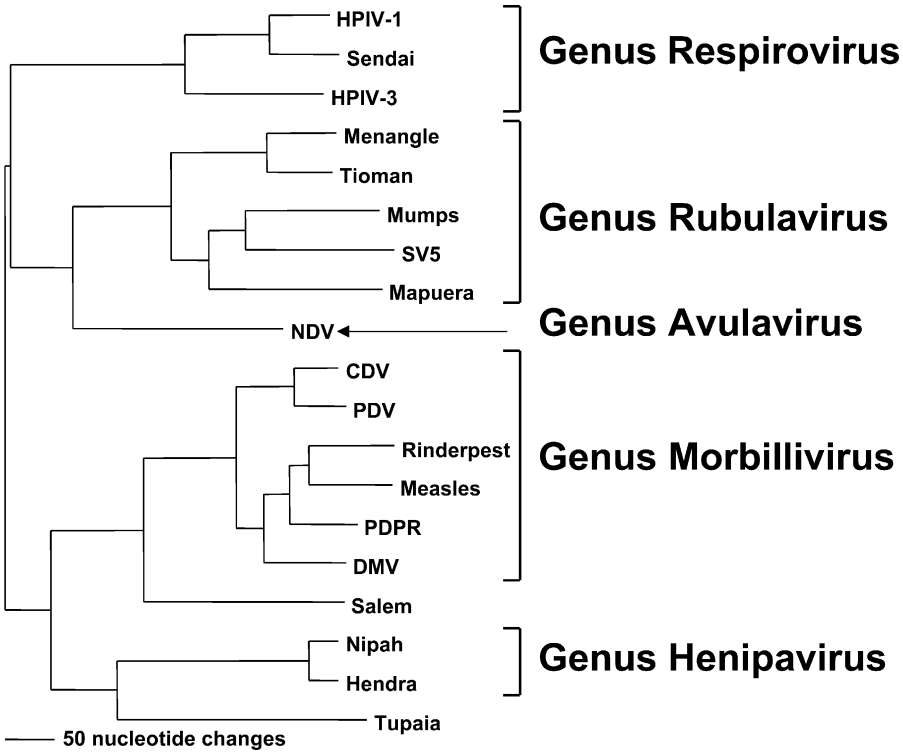

Figure 2 Phylogenetic analysis of the N ORFs from members of the subfamily *Paramyxovirinae*. Brackets identify the five genera. A phenogram of the N ORFs of members of the subfamily *Paramyxovirinae* was derived using maximum parsimony analysis with PAUP 4.02. Abbreviations and accession numbers: Human parainfluenza virus-1 (HPIV-1), D01070; Sendai, X00087; HPIV-3, D10025; canine distemper virus (CDV), AF014953; phocine distemper virus (PDV), X75717; rinderpest virus (RPV), X68311; MV, K01711; dolphin morbillivirus (DMV), X75961; Newcastle disease virus (NDV), AF064091; goose paramyxovirus (GP), AF473851; HPIV-4b, M32983; HPIV-4a, M32982; Tioman, AF298895; Menangle, AF326114; HPIV-2, M55320; simian virus 5 (SV5), M81442; mumps, D86172; NV-UMCC1, AY029767; NV-Malaysia, AF212302; hendra virus, AF017149; tupaia paramyxovirus, AF079780; Mossman virus, AY286409; and Salem virus, AF237881.

members of the family *Paramyxoviridae* (Harcourt *et al*, 2000; Wang *et al*, 2001).

The G proteins of the henipaviruses differ from the H or HN glycoproteins of other paramyxoviruses in that they have no known hemagglutinin or neuraminidase activities (Harcourt *et al*, 2000; Yu *et al*, 1998a). The G proteins of henipaviruses act in concert with the F proteins to mediate cell infection. The G protein presumably binds to an unidentified cellular receptor. Receptor binding allows the F protein to mediate fusion with the host cell membrane to permit virus entry. As with many paramyxoviruses, both the F and G proteins of henipaviruses are necessary for membrane fusion (Bossart *et al*, 2001, 2002; Guillaume *et al*, 2004; Tamin *et al*, 2002). In other paramyxoviruses, the surface glycoproteins are the main targets for neutralizing antibodies. Recombinant vaccinia viruses expressing NV F and G illicit neutralizing antibodies against NV and protect Syrian hamsters against lethal.... antibodies to F or G also provided passive protection in the hamsters challenge model (Tamin *et al*, 2002; Guillaume *et al*, 2004).

It is assumed that the henipaviruses follow the same replication strategy as other paramyxoviruses, and data from recent studies are have verified that assumption (Figure 1B). Because the genomic RNA of henipaviruses is negative sense, transcription must occur before viral proteins are expressed. The transcription complex consisting of the L and P proteins initiates transcription at the 3′ terminus of the genomic RNA. Monocistronic capped and polyadenylated mRNAs are synthesized for each viral gene. An intergenic region consisting of a GAA trinucleotide exists between each gene. Immediately upstream of the gene junctions, the transcription complex encounters a stop signal and then either proceeds to initiate transcription of the next gene downstream or disengages from the viral RNA to reinitiate transcription at the 3′ terminus. Therefore, the relative abundance of a viral transcript varies inversely with its distance from the 3′ terminus of the genome. As free N accumulates in the cytoplasm, the polymerase switches from transcription to genome replication and reads through the stop signal and intergenic regions to synthesize full-length plus sense viral RNA that serves as a template for synthesis of negative sense, genomic RNA (Bellini *et al*, 1998; Lamb *et al*, 2001).

Epidemiology and transmission

Fruit-eating bats appear to be a natural reservoir for the henipaviruses and humans are infected via intermediate hosts such as horses or pigs, by exposure to infected fruit bats or material contaminated by infected bats, or by direct human-to-human transmission. HV was isolated from fruit bats in Queensland, Australia (Young *et al*, 1996; Halpin *et al*, 1999, 2000) and transmission to horses may have occurred through the ingestion of material contaminated by the urine or infected fetal tissue of infected fruit bats (Halpin *et al*, 1999; Field *et al*, 2000). Neutralizing antibodies to NV were found in four fruit bat species and one insectivorous bat species in peninsular Malaysia (Yob *et al*, 2001), and antibodies to NV have been detected in Cambodian bats (Olson *et al*, 2002). NV was isolated from Malaysian fruit bats roosting on Tioman Island (Chua *et al*, 2002). Though antibodies to NV were detected in fruit bats from the outbreak areas of Bangladesh in 2004, an intermediate animal host was not identified.

Although NV is excreted in respiratory secretions and urine of patients (Chua *et al*, 2001), a survey of health care workers in Malaysia demonstrated no evidence of human-to-human transmission (Mounts *et al*, 2001). However, investigations of the more recent NV outbreaks in Bangladesh identified new transmission patterns. No amplifying host was identified during the outbreaks of NV in Bangladesh; therefore it is likely that the virus was transmitted directly or indirectly from bats to humans. In fact, human-to-human transmission of NV was also documented during the outbreak in Faridpur, Bangladesh, in 2004 (ICDDRB, 2004a, 2004b; WHO, 2004).

Clinical and pathological manifestations

The onset of NV disease in humans is abrupt, usually with the development of fever and severe encephalitis. Fever (97%), headache (65%), dizziness (36%), vomiting (27%), and reduced level of consciousness (21%) were the most common clinical features noted during the outbreaks in Malaysia and Singapore (Goh *et al*, 2000). The disease in 3 of the 11 patients in Singapore presented as an atypical pneumonia, with fever and infiltrates on chest radiography (Paton *et al*, 1999). Acute respiratory distress was also noted in many patients during the NV outbreak in Bangladesh in 2004 (ICDDRB, 2004a, 2004b). The case fatality rates were 40% in Malaysia and 75% in Bangladesh and the difference in rates most likely reflect differences in the availability of appropriate supportive care. Residual neurologic deficits were noted in 10% to 15% of patients with NV infection, including a vegetative state, cognitive impairments, and cerebellar disabilities (Paton *et al*, 1999; Goh *et al*, 2000; Sarij *et al*, 2000). Recurrence of neurologic dysfunction was seen in some patients, including neurologic relapse with seizures and/or cognitive impairment or focal signs such as isolated cranial nerve dysfunction.

The exact incubation period of NV disease in humans is not known but ranged from several days to 2 months, but was 2 weeks or less in the majority of patients. A multiorgan vasculitis associated with infection of endothelial cells was the main pathologic feature of NV infection (Parashar *et al*, 2000), with infection being most pronounced in the central nervous system where a diffuse vasculitis characterized by segmental endothelial cell damage, mural necrosis, karyorrhexis, and infiltration with polymorphonuclear leukocytes and mononuclear cells is noted. Immunohistochemistry (IHC) assays showed intense staining of endothelial and parenchymal cells and multinucleate giant cells characteristic of paramyxovirus infections are observed in the vascular endothelium. (Figure 3A). However, evidence of endothelial infection and vasculitis were also observed in other organs, including lung, heart, spleen, and kidney. NV has been isolated from cerebrospinal fluid, tracheal secretions, throat swabs, nasal swabs, and urine specimens of patients (Goh *et al*, 2000; Chua *et al*, 2001).

Although pigs showed extensive infection of the upper and lower airways (Figure 3B), with evidence of tracheitis, and bronchial and interstitial pneumonia, the mortality rate was less than 5%. A harsh, nonproductive cough (called the mile long cough) was a prominent clinical feature but other signs such as lethargy or aggressive behavior indicated some neurological involvement (Chua *et al*, 2000; Hooper *et al*, 2000). Serologic studies demonstrated evidence of infection among other species of animals, including dogs and cats (Chua *et al*, 2000; Hooper *et al*, 2000), on and near farms with NV-infected pigs, though it is unclear whether humans were at risk from exposure to infected animals other than pigs (Goh *et al*, 2000; Parashar *et al*, 2000).

Because HV and NV are biosafety level (BSL)-4 agents, data from experimental infections are limited and little is known about clinical disease and associated pathology in the natural hosts of HV and NV. Natural or experimental HV infections of bats are asymptomatic though the bats seroconvert and viral antigen and some live virus can be detected (Williamson *et al*, 1998; Halpin *et al*, 2000; Field *et al*, 2001). Horses and cats naturally infected with HV show clinical signs that include depression, anorexia, profuse nasal discharge, and labored breathing with pulmonary edema and congestion and HV can be isolated from the urine of infected animals (Williamson *et al*, 1998; Field *et al*, 2001).

Infection of golden hamsters (*Mesocricetus auratus*) with NV reproduces the pathogenesis of acute NV infection in humans, and could provide an animal model for studying the pathogenesis of NV. Infection by the intranasal or intraperitoneal routes caused a fatal neurological disease associated with severe pathological lesions in the hamster brain. Viral antigen and

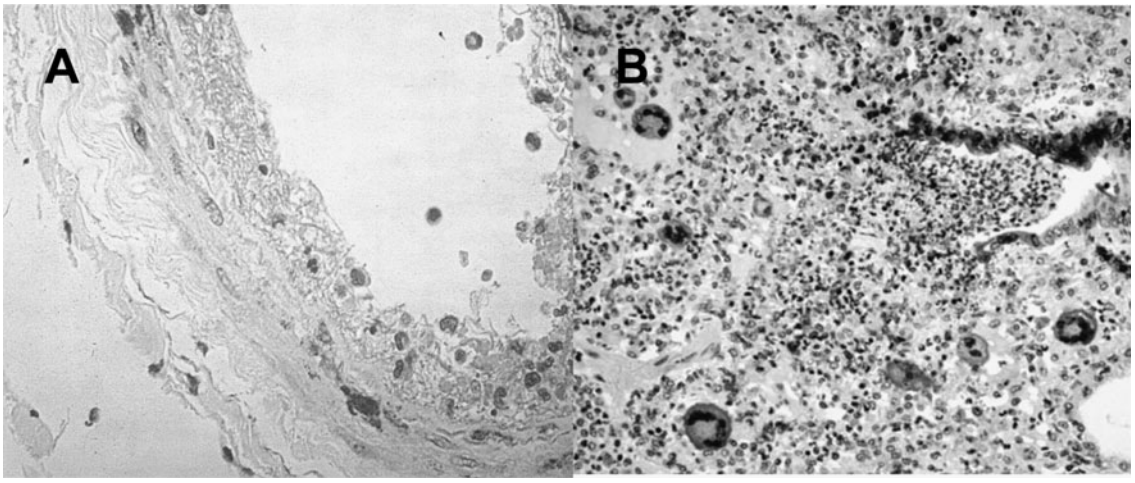

Figure 3 Detection of NV antigens in tissue samples by immunohistochemical staining. **A**, Section of human brain; **B**, Section from porcine lung after staining with hyperimmune mouse antiserum to NV.

RNA were detected in neurons, lung, kidney, and spleen, and virus and/or viral RNA could be recovered from most organs and urine, but not serum. NV was also detected in endothelial cells (Wong *et al*, 2003).

Control

Because interruption of transmission NV from the reservoirs to intermediate hosts or directly to humans is difficult, early identification of infected animals and humans and use of appropriate personal protective equipment in health care and agricultural settings are the keys to prevention. Because person-to-person transmission of NV virus has been documented, those in contact with patients, including health care workers, should use standard droplet precautions during contact with secretions, excretions, and body fluids of patients.

No vaccines or antiviral drugs are currently available for NV. During the NV outbreak in Malaysia, patients receiving ribavirin either orally or intravenously showed a lower mortality rate (Chong *et al*, 2001).

Laboratory diagnosis

Analysis of serum samples from outbreaks indicated that NV generates a humoral immune response in humans. Immunoglobulin M (IgM) was present in serum shortly after the onset of NV infection and nearly all patients were antibody-positive by the third day (Ramasundrum *et al*, 2000). IgG was detected 10% to 29% of NV infected patients within the first 10 days of illness, and in 100% of patients after 17 to 18 days.

Because of their ability to cause severe disease in animals and humans, work with live NV must be conducted at BSL-4. Enzyme-linked immunosorbent (ELISA) assays to detect IgG and IgM antibodies are routinely used to detect HV and NV infections. These assays often use inactivated or antigens expressed by recombinant DNA technology and, therefore, have the advantage that they do not need to be conducted at BSL-4. Also, IgG antibodies can be detected by using standard serum neutralization tests. Immunohistochemistry has proven extremely useful for detecting NV antigens in fixed tissue samples. Both HV and NV can be isolated on Vero-E6 cells from cerebrospinal fluid, nasal samples and urine samples from infected individuals (Goh *et al*, 2000; Chua *et al*, 2001). Various reverse transcriptase–polymerase chain reaction (RT-PCR) assays have been used to detect RNA from HV and NV in a variety of clinical samples and tissues (Halpin *et al*, 2000; Daniels *et al*, 2001; Guillaume *et al*, 2004).

Conclusions

The fruit bats that have been implicated as a reservoir for NV are found in an area that extends from northern India eastward to include Bangladesh, Myanmar, Thailand, Malaysia, Cambodia, Indonesia, Papua New Guinea, and eastern Australia. Therefore, it is very likely that sporadic outbreaks of NV will continue to occur. Recent evidence has suggested that an amplifying animal host is not necessary and that at least some human-to-human transmission is possible. To prevent these outbreaks, it is critically important to fully understand the distribution of the natural reservoir(s) for NV and the environmental and epidemiologic circumstances that favor transmission to humans. Because NV can cause severe disease in both humans and animals of agricultural importance, it is potential agent of bioterrorism. Therefore, NV

remains a significant threat to both humans and agriculture and it will be essential to significantly expand laboratory surveillance capacity to detect NV, particularly in southern Asia. Finally, fully understanding the pathogenesis of NV in humans and animal hosts will allow for the development of immunoprophylactic and therapeutic measures to prevent or control infection.

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