

Pathology of Henipavirus infection in humans and hamster model

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Abstract

Hendra and Nipah viruses (genus: *Henipavirus*) are novel paramyxoviruses that emerged to cause severe human and animal disease. Studies in both humans and animals suggest that both viral infections are associated with similar pathologies. This is probably related to the common viral receptors that henipaviruses employ to infect the cell. The blood vessels and central nervous system tissues were particularly susceptible. A dual pathogenetic mechanism of vasculitis-associated thrombosis/microinfarction and direct parenchymal cell infection contributed to acute tissue injury. A unique relapsing encephalitis may also complicate henipavirus infection.

INTRODUCTION

The newly created genus *Henipavirus* (family *Paramyxoviridae*) consists of the Hendra virus (HeV) and the Nipah virus (NiV), both emerging viruses that have caused serious illness in humans and animals. HeV was discovered in 1994, in Australia following an outbreak in horses and people in close contact with sick animals.¹ NiV was first isolated in 1999 in Malaysia following a much larger outbreak of infection in pigs and humans.^{2,3} Both HeV and NiV are accidental zoonotic infections whose natural hosts are pteropid bats (“flying foxes”) found mainly in Australia and Asia.^{4,5} This review focuses on current knowledge and updates on henipavirus infectious pathology and pathogenesis.

NIPAH VIRUS INFECTION

The first known human NiV outbreak was from 1998-1999 in pig farms in Malaysia in which it was estimated a total of 350 were infected.⁶ In a series of 265 cases of acute NiV encephalitis in Malaysia there were 105 fatalities (40% mortality).⁷ The outbreak spread to Singapore where 11 abattoir workers became infected. In Bangladesh and India there were several NiV outbreaks starting 2001 that appears to be still ongoing.^{8,9} More than 120 people were reported to be infected in the Indian subcontinent so far. In Malaysia and Singapore, epidemiological studies showed that direct contact with pigs or pig products was responsible for human transmission.^{7,10-12} Although viral transmission to health care workers was thought to be low in

Malaysia^{13,14}, in Bangladesh and India, human-to-human transmission seemed to play an important role.^{8,9} Moreover, contaminated date palm juice was shown to be important for bat-to-human transmission in Bangladesh.¹⁵ Mortality in the Indian subcontinent was about 70%.

Human pathology

The clinical manifestations ranged from fever, headache, drowsiness, cough, to a fatal acute encephalitic syndrome.^{3,16-18} Autopsy studies showed acute NiV infection to be a systemic infection.¹⁹ The earliest lesion seemed to be the formation of the relatively uncommon endothelial multinucleated syncytia. More frequently, vessels showed endothelial ulceration, inflammation (intramural neutrophils, macrophages, etc) and fibrinoid necrosis. Associated thrombosis and vessel occlusion were often observed. Viral antigens were immunolocalized to endothelium, syncytia and tunica media. Furthermore, viral nucleocapsids were identified in the endothelium by electron microscopy.²⁰

The brain was most severely involved by disseminated vascular lesions.²¹ Around vasculitic vessels there were often small areas of necrosis/ischemia, referred to as necrotic plaques. Surviving neurons around grey matter plaques may reveal viral inclusions, antigens/RNA and nucleocapsids. Hence, necrotic plaques were probably due to a combination of microinfarction and neuronal infection. Inflammatory perivascular cuffing and neuronophagia could be observed in some areas. Glial cell infection was rare.

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Vasculitis, parenchymal lesions and viral antigens could also be found in the lung, kidney, heart and other organs.²¹ In the lung, fibrinoid necrosis, vasculitis, alveolar multinucleated giant cells were observed. Kidney pathology was characterized mainly by vasculitis and glomerular lesions. Multinucleated syncytia probably arising from podocytes was occasionally noted.

Animal pathology

The golden hamster has been reported to be a good model for acute NiV infection.²² Infected hamsters developed neurological clinical features and evidence of systemic vasculitis, multi-organ parenchymal and central nervous system (CNS) neuronal infection. Most features in human infections were found in the hamster model. The main pathology in the pig was found in the respiratory system and meninges.²³⁻²⁵ There was evidence of airway inflammation and pneumonia. In contrast to infection in humans and hamsters, encephalitis was rare.²⁵

HENDRA VIRUS INFECTION

The first known human case of HeV infection was from MacKay, Australia, in August 1994 but this was not recognised until after infection and death of another case from Hendra, a month later. So far 6 people have been infected, with 3 fatalities. All cases have had close contact with infected horses.²⁶⁻²⁹ The case from Hendra presented clinically as an acute respiratory infection^{26,28}, while the second fatality from MacKay presented initially with headache, drowsiness and meningitis, and died 13 months later from a full blown encephalitis.²⁸ The last reported outbreak of HeV infection in horse and human was in 2004.²⁷ So far, HeV outbreaks have not been reported outside Australia.

Human pathology

Much less is known about the pathology of human HeV infection than NiV. In the fatal case of acute HeV infection, despite apparent absence of neurological manifestations, vasculitis in the brain and also extraneural organs was demonstrated. In addition, viral antigens were detected in vascular walls, neurons, ependyma, glomeruli, and alveolar pneumocytes.³⁰ The lung showed intense inflammation consisting of focal necrotising alveolitis, giant cell and syncytial formation and viral inclusions.²⁶ In the case of relapsed HeV encephalitis from Mackay, pathological evidence

of encephalitis was confirmed.²⁸ Viral antigen/RNA were demonstrated in neurons but there was no evidence of systemic vasculitis.³⁰

Animal pathology

Studies of acute HeV infection in horses, guinea pigs and cats^{1,23,31} showed that systemic vasculitis could occur. Acute encephalitis and neuronal infection in guinea pigs was consistent with acute human HeV. Recent studies of acute HeV infection in hamsters confirmed neurotropism and systemic vasculitis and appears to be similar to human acute HeV infection.³²

PATHOGENESIS AND SEQUELE OF HENIPAVIRUS INFECTION

In both NiV and HeV human and animal pathology strongly suggests that the pathogenesis is similar and that tissue injury arose from vasculitis-induced microinfarction and direct parenchymal infection. This dual pathomechanism has not been described in other viral infections. The sharing of viral receptors Ephrin B2 and B3 by henipaviruses is consistent with this.³³⁻³⁶

For reasons unknown, 8% of survivors suffered neurologic relapses (relapsed NiV encephalitis) after acute NiV encephalitis.^{37,38} About 3% who were either asymptomatic or had mild non-encephalitic illness initially, also developed similar neurologic episodes (late-onset NiV encephalitis). Clinicopathological findings suggested that relapsed and late-onset NiV encephalitis is the same disease process that was distinct from acute encephalitis.^{37,39} The presence of neuronal viral antigens/RNA in autopsy cases of relapsed/late-onset NiV encephalitis suggested that it was due to recurrent infections rather than post infectious demyelination.³⁷ Relapsed NiV encephalitis appeared analogous to the single case of relapsed HeV encephalitis.^{28,30}

In conclusion, the pathology and pathogenesis of Henipavirus infection in both humans and animals appear to be similar.

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