Nipah and Hendra viruses: recent advances in pathogenesis

KT Wong

Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
■ Tel.: +60 379 492 064 ■ Fax: +60 379 556 845 ■ wongkt@um.edu.my

“Currently, several vaccine and treatment modalities have already been tested and some appear to work ... A greater understanding of the viral pathogenesis of henipaviruses should lead to other significant clinical breakthroughs...”

In 1998, an outbreak of human acute encephalitis in Malaysia led to the discovery of a novel paramyxovirus named Nipah virus (NiV) [1]. Subsequently, outbreaks were also reported in Bangladesh and India. So far, more than 500 people have been infected with a mortality of 40–70% [2–5]. NiV is closely related to Hendra virus (HeV), discovered in Australia in 1994 [6]. Hitherto, there are only seven known human HeV cases. Both viruses have been placed into the newly created genus *Henipavirus*, within the same family as the measles virus, *Paramyxoviridae* [7].

The natural host of henipaviruses is the pteropid or fruit bat, whose range extends through Africa, Asia–Oceania and Australia. In the NiV outbreaks in Malaysia and Singapore, the intermediate host was the pig, while in Bangladesh and India, direct bat–human and human–human transmissions occurred [3,8]. Acute NiV infection may be asymptomatic; symptomatic cases present with fever and headache or acute encephalitis that is often associated with coma. In patients who recovered from acute infection, approximately 5–8% relapsed or developed late-onset NiV encephalitis, which was thought to be clinically distinct from acute NiV encephalitis [9]. HeV infection is also associated with acute and relapsing encephalitis [10]. In general, brain imaging in acute encephalitis showed multiple discrete lesions whereas in relapsing encephalitis, the lesions were more confluent [11,12].

Most of the evidence for the pathogenesis of human henipavirus infection is derived from autopsy studies of NiV infection [13]. In acute NiV infection, systemic vasculitis, discrete, plaque-like parenchymal necrosis and inflammation are found in most major organs, particularly in the CNS. Vascular endothelial damage resulted in thrombosis, vascular occlusion, ischemia and microinfarction. Viral antigens and nucleocapsids are immunolocalized to

the vascular wall. Viral inclusions, nucleocapsids, antigens and RNA were also detected in extravascular parenchymal cells, especially in neurons. The pathogenesis of acute NiV infection appears to be a unique dual mechanism of vasculitis-induced thrombosis, ischemia/microinfarction and direct parenchymal cell infection. Autopsy evidence from the much rarer acute HeV infection suggests that the same pathogenetic mechanisms apply [10].

The pathogenesis of acute henipavirus infection in humans has been confirmed in many infection studies in animal models using the hamster, guinea pig, cat, pig, ferret and monkey [14–21]. Generally, similar to in human infections, there is systemic vasculitis and subsequent vessel wall infection, and also evidence of extravascular parenchymal cell infection.

In relapsing henipavirus encephalitis, CNS-limited lesions consisted of mildly inflamed, vacuolated necrotic lesions merging with confluent areas of more extensive parenchymal necrosis and increasing inflammation [10,13]. There were neuronal viral inclusions, antigen/RNA and nucleocapsids but vasculitis was absent throughout. In NiV, some lesions had a distinctive concentric or wave-like morphology [WONG KT, UNPUBLISHED DATA]. These findings suggest that relapsing henipavirus encephalitis is a recurrent *de novo* infection rather than postinfectious encephalitis. Moreover, recurrence is unlikely to arise from extraneural foci because that would involve viremic spread to the CNS and almost certain vascular infection and vasculitis. Why does relapsing encephalitis occur? If a parallel may be drawn to subacute sclerosing panencephalitis, which is associated with mutant measles virus infection, then viral mutation is one possibility. It is possible that certain mutations may allow the virus to remain within the neurons, spread via interneuronal connections and escape the immune response. So far, no

mutations have been discovered [YAIWK, WONG KT, UNPUBLISHED DATA]. The other possibility is, like measles, immunosuppression could occur with acute henipavirus infection that allows small virus foci to remain viable [22]. Over time, the virus may spread slowly to cause relapsing encephalitis. Whether or not these recurrences involve further immunosuppression by the virus or other unknown factors remain to be investigated. The time interval from subsidence of acute infection to the first symptoms of relapsing encephalitis may vary from weeks to years [9,23]. It is possible that acute encephalitis may continue as relapsing encephalitis without a significant interval, as was suggested by some acute NiV cases from Bangladesh, in which brain magnetic resonance scans demonstrated confluent lesions more typical of relapsing encephalitis than the discrete lesions of classical acute NiV encephalitis [24]. Immune modulation and its possible role in various manifestations of henipavirus infection and their progression therefrom need to be investigated. Whether or not a person's particular genotype could impact susceptibility to infection is unknown. There is currently no animal model for relapsing henipavirus encephalitis.

That henipaviruses share common pathogenetic mechanisms, in humans at least, is not surprising since both viruses were reported to use the same ephrin B2 and B3 ligands as virus receptors [25,26]. However, it is still possible that

there are significant differences in the pathogenesis of NiV and HeV. This should be further investigated in animal models as the number of human HeV cases are still relatively small. It is uncertain if there is a role for direct transnasal viral transmission to the human CNS, as was shown in pigs [16]. Last, but not least, henipaviruses with different genotypes within the same species may yet have differences in pathogenesis, therefore animal studies with NiV from Bangladesh, which has significant nucleotide differences from the Malaysian isolate, could prove interesting, particularly if combined with studies using infectious clones [27].

Currently, several vaccine and treatment modalities have already been tested and some appear to work, at least in animal models [19,20,28]. A greater understanding of the viral pathogenesis of henipaviruses should lead to other significant clinical breakthroughs in the future.

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Affiliation

- KT Wong
Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
Tel.: +60 379 492 064
Fax: +60 379 556 845
wongkt@um.edu.my