Nipah Virus Encephalitis

24

Feng Chen, Dawei Zhao, and Zengxin Jiao

Nipah virus encephalitis is a zoonotic infectious disease caused by *Nipah* virus (NiV), which is categorized into the genus of *Henipavirus* and the family of *Paramyxoviridae*. NiV is a new zoonotic virus that was firstly isolated from deceased patients in Nipah, a village in Perak, Malaysia, in the late 1990s. The virus has been mainly found in Malaysia, Bangladesh, and their surrounding areas in Southeast Asia. It has no pathogenicity to bats but is capable of infecting pigs. In addition, it is highly pathogenic to humans. NiV can cause severe encephalitis and respiratory diseases in animals and humans, with high incidence and mortality. The mortality rate in patients with NiV infection is up to 40–70 %, and therefore, the virus has been listed as one of the biosafety level 4 (P4), the most dangerous, pathogens.

24.1 Etiology

NiV is an RNA virus, which has highly homogeneous genome to *Hendra* virus (HeV) that was firstly found in Australia in 1994. The genomes of these two viruses have 2,000 more nucleotides than other viruses in the family of *Paramyxoviridae*. The protein antigenicity of these two viruses is also similar; both of which are classified in the genus of *Henipavirus* and the family of *Paramyxoviridae*. However, they are not identical. Among the viruses in the family of *Paramyxoviridae*, both NiV and HeV are the closest to measles virus. However, due to the long genome of both NiV and HeV and their respective unique sequence, both of their reservoir hosts are bats, and they can infect a variety of hosts. HiV and NeV have been separately classified into a new genus in the subfamily of *Paramyxoviridae* and the family of *Paramyxoviridae*, namely, the genus of *Henipavirus*.

NiV can grow in any of mammalian cell line to cause syncytial-like lesions but cannot grow in insect cell line. The virus can grow well in Vero, BHK, and PS cells but is unstable in external environment. It is sensitive to temperature, disinfectants, and detergents, which can be destroyed at a temperature of 56 °C for 30 min. In addition, it can be inactivated by commonly used disinfectants or detergents.

24.2 Epidemiology

24.2.1 General Introduction to Its Prevalence

During the period from 1998 to 1999, large-scale outbreak of NiV infection in pigs occurred in Malaysia, which resulted in 257 cases of human infection including 105 cases of death. Another two events of NiV infection occurred in Malaysia in June 2000. Meanwhile, due to the import of pigs from Malaysia, 11 cases of NiV infection in humans was reported, including 1 case of death. During the period from 2001 to 2005, five events of NiV infection in humans were reported consecutively, with a total of 69 death cases.

During the prevalence of NiV infection in Malaysia, NiV carried by fox bats may infect pigs with a tiny probability, which then proliferated in pigs in a large quantity and rapidly spread to other pigs via contacts. Humans were then infected via close contacts to these pigs. However, in the events occurring in Bangladesh, most of the NiV infected people had no history of close contacts to pigs, and pigs in these areas also had no sign of NiV infection. Therefore, pigs did not play an important role in the events occurring in Bangladesh. But the initial route of transmission for human infection remains unknown. In the events occurring in

F. Chen (✉) • D. Zhao • Z. Jiao
Department of Radiology, Beijing You'an Hospital, Capital Medical University, Beijing, China
e-mail: cfqlx@sogou.com

H. Li (ed.), *Radiology of Infectious Diseases: Volume 1*, DOI 10.1007/978-94-017-9882-2_24

Malaysia, no evidence has been found to prove spreading of the virus between humans; while in the events occurring in Bangladesh, conclusive evidence has been found to prove spreading of the virus from person to person.

24.2.2 Source of Infection

Although NiV can infect a variety of livestock by fruit bats, pig is still the main source of infection. Recent reports have demonstrated that NiV can spread via contaminated food or spread from person to person.

24.2.3 Route of Transmission

NiV possibly spreads via body fluid or blood, such as contacts to body fluid from patients. The routes of transmission may include direct contact to urine, body fluid, or tracheal secretions from infected pigs, sharing needle, artificial fertilizing, and vertical transmission from mother to infant. The transmitting route of NiV from person to person is not the major route of its transmission. Mosquitoes and other insects are not the media for its spreading. Although other natural hosts such as hounds, cats, Percheron, wild pigs, and rats could be infected, the virus fails to spread widely due to rapid death of these infected animals. In the outbreaks of NiV infection by humans, pig plays an important role, which spreads the virus via contacts or airborne transmission. After NiV infection by pigs, the virus can multiply in their bodies in large quantities. Viremia may persist for a long period of time, during which the virus may be spread externally via respiratory tract, urine, feces, and saliva. In addition, starlings such as mynas and grackles seek food in the piggery, which often peck ticks on the back of pigs and fly within one piggery or among piggeries. Therefore, starlings may be another route of transmission for NiV.

24.2.4 Susceptible Population

Workers working in piggeries or slaughterhouses have much more chances to contact to diseased pigs due to their job. Therefore, this population is the high-risk population for NiV infection.

24.3 Pathogenesis and Pathological Changes

24.3.1 Pathogenesis

NiV interacts with the host cell surface receptor ephrin B2 via G protein to recognize and adhere to the surface of host cells. Ephrin B2 is ligand of the subgroup Eph B in receptor tyrosine kinases (RTKs). Eph and its ephrin ligands play an important role in the processes of CNS development, angiogenesis, and tumor formation. Ephrin B2 is mainly expressed in neuronal cells, smooth muscle cells, arterial endothelial cells, and capillaries, which is consistent to the tropism of NiV to endothelial cells and the nervous system. Ephrin B2 is conservative in mammals, which may be related to the fact that many mammals are susceptible to NiV. In addition, ephrin B3, one of the homogeneous proteins of ephrin B2, is also capable of independently facilitating NiV gaining its access into cells, which is possibly one of the NiV receptors. After the invasion of NiV into the endothelial cells, it replicates itself rapidly and affects the synthesis of interferon and its functions under effects of multiple proteins such as P, V, W, and C protein to evade the defense system of the host. Meanwhile, it fuses with endothelial cells under the effects of proteins F and G to form endothelial syncytium, with following rupture of the cell to release the virus. The emergence of endothelial syncytium is characteristically an NiV infection, with a detection rate of 25 % by pathological examination in clinically diagnosed cases. In addition, NiV can also infect neurons directly, where it grows and proliferates to cause neurological symptoms.

24.3.2 Pathological Changes

NiV infection can involve any system of human body. By autopsy, the brain is found to be the most seriously affected organ, with possible involvements of the gray matter, white matter, basal ganglia, cerebellum, brain stem, and spinal cord. Other organs may also be involved, including the lungs, heart, and kidneys. The basic pathological changes are multiple organs vasculitis and endothelial cell inflammation. Vasculitis commonly occurs in minor arteries, arterioles, capillaries, and venules, which is characterized by vascular wall necrosis, thrombosis, and infiltration of inflammatory cells like leukocytes and monocytes. The infection of CNS shows extensive and scattering small necrotic foci. By immunohistochemical assays, NiV antigen can be detected in CNS tissues, especially in vascular endothelial cells with vasculitis, endothelial syncytium, and parenchymal cells. A small amount of viral antigens can also be detected in other tissues. The occurrence of death in patients with NiV infection is commonly from extensive focal infarction of brain tissues caused by atrophy of large quantities of infected neurons.

24.4 Clinical Symptoms and Signs

NiV has an incubation period of 1–3 weeks in the human body. Clinically, the patients commonly experience fever and headache for 3–14 days. After that, symptoms of drowsiness

and systemic myalgia occur. There are also obvious symptoms of encephalitis and/or meningitis such as neck rigidity, varying degrees of psychiatric symptoms, cerebellar dysfunction, weak or absent deep tendon reflexes, limb paralysis, clonic convulsion, language impairment, visual hallucinations, and auditory hallucination. In 24–48 h, the patients may further develop into coma. The characteristic symptoms of NiV infection are cervical and abdominal muscle spasms. The conditions have varying severity, with commonly neurological symptoms and rarely accompanying respiratory symptoms, hypertension, and tachycardia. Some patients may experience delayed onset of clinical symptoms, with delayed onset of neurological symptoms. In some patients, the neurological symptoms may even occur 4 years after the infection, and during this period, some cases may have no encephalitic symptom or even be asymptomatic. There is also rarely occurring relapse of acute encephalitis after its recovery, which is commonly found several months to 2 years after initial infection. In some cases, its relapse occurs even 4 years after the initial infection. The relapse may be related to persistent survival of the virus in the CNS tissues.

24.5 Nipah Virus Encephalitis Related Complications

In severe cases, Nipah virus encephalitis can be complicated by diseases like septicemia, gastrointestinal bleeding, and kidney impairment. The rarely found complications include pulmonary embolism and atrial fibrillation.

24.6 Diagnostic Examinations

24.6.1 Laboratory Tests

24.6.1.1 Routine Blood Test and Biochemical Test

Lymphocyte count and platelet count decrease. Blood sodium level decreases. EFG increases. The levels of aspartate aminotransferase and alanine aminotransferase may mildly increase.

24.6.1.2 Immunologic Assays

Serum neutralization test is the standard serological test for NiV detection, but the test should be performed in the P4 laboratory. IFA and ELISA can be performed in common laboratories, with findings of specific IgM and IgG antibodies of the virus in the serum or cerebrospinal fluid specimen. Immunohistochemical method can be applied to detect the virus antigen from multiple organ tissues such as the brain, lungs, and kidneys. However, in some tissues, the virus antigen can be cleared in the early stage of the disease, while the virus antigen has a higher positive rate from tissues of the CNS, which is 3–4 times as high as that from the lungs or kidneys.

24.6.1.3 PCR Detection for Virus Gene

RT-PCR can be applied to detect the virus RNA from cerebrospinal fluid, serum, plasma, and brain tissue, with M or N gene of the virus commonly detected.

24.6.1.4 Virus Culture and Isolation

The virus culture and isolation is the basic and the most reliable way for the diagnosis of NiV infection. NiV has cytopathic effect on many cells, including ATCC and CCL81 cells. Such infected cells can be detected and isolated from cerebrospinal fluid, respiratory secretions, and urine, which can be then cultured in Vero or BHK cells for isolation. But these procedures should be performed in P4 laboratory.

24.6.1.5 Cerebrospinal Fluid Examination

At the early stage of the disease, 75 % of the cases show abnormalities of the cerebrospinal fluid, specifically elevated protein above 4.45 g/L. WBC count increases and lymphocyte count increases to above 6×106/L; sugar level is normal or elevates, and cerebrospinal fluid pressure slightly increases. The findings of cerebrospinal fluid examination have no significant relationship with the severity of the conditions. However, successful isolation from the cerebrospinal fluid is related to the mortality rate. Antibodies DHC and DHI against NiV can be found positive in specimen of serum or cerebrospinal fluid.

24.6.2 Electroencephalography

By electroencephalography, the waves of periodic epileptiform discharge can be found, which exceed those from bilateral temples.

24.6.3 Diagnostic Imaging

24.6.3.1 Chest X-Ray

Chest X-ray is commonly applied for the diagnosis of pulmonary lesions.

24.6.3.2 CT Scanning and MR Imaging

CT scanning and MR imaging are commonly applied for the diagnosis of intracranial infections. The sensitivity to intracranial lesions by MR imaging is superior to that by CT scanning, which is a favorable radiological examination for the diagnosis of NiV encephalitis. By MR imaging, the

FLAIR sequence can display intracranial lesions earlier, with better defined details and range of the lesions.

24.7 Imaging Demonstrations

NiV encephalitis shares general imaging demonstrations of virus encephalitis and has its own characteristic imaging demonstrations.

24.7.1 General Imaging Demonstrations of Viral Encephalitis

1. The lesions are bilateral and multiple. Unilateral singular lesion is rarely found.
2. The lesions may involve the frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, thalamus, brain stem, and various parts of cerebellum. Both the gray and white matters can be involved, which is more common in the bilateral temporal lobes, frontal lobes, and parietal lobes.
3. The lesions can be demonstrated in large flakes, small flakes, and mass flakes.
4. Accompanying bleeding can be found within the lesions.
5. Generally, the space-occupying effect of the lesions is not obvious.
6. T_1WI of MRI demonstrates slightly lower or equal signal; T_2WI demonstrates slightly higher or high signal; FLAIR sequence demonstrates high signal.
7. Contrast imaging demonstrates no obvious enhancement, linear enhancement, spots of enhancement, flakes of enhancement, nodular enhancement, gyrus-like enhancement, or accompanying meningeal enhancement.

24.7.2 Nipah Virus Encephalitis

In the acute and late stages of the disease, MR imaging displays the lesions mostly in surrounding areas of the brain parenchyma (subcortical), surrounding areas of basal cistern, brain stem, interface of gray and white matters, and periventricular region. They are multiple small focal lesions with a diameter of 2–7 mm in a round or strip-like shape. T_2WI and FLAIR demonstrate high signal, with no surrounding edema. In the cases with extensively disseminated lesions across the brain parenchyma, large mass of lesions is rarely found. And nearly half of the patients have damaged cerebral cortex. As the lesions develop into the late stage, some patients may manifest stale hemorrhage. By FLAIR sequence, no high signal can be found in the subarachnoid space. Contrast imaging in the acute stage demonstrates no enhancement and no obvious meningeal enhancement (Figs. 24.1, 24.2, 24.3, 24.4, 24.5, and 24.6). The main pathological changes include thrombosis caused by vasculitis, which develops into extensive microthrombosis across the whole brain. In some patients, MR imaging in the acute stage and in the late stage has no significant difference. However, MR imaging demonstrates relapsed and delayed encephalitis as obviously fused lesions in the cortex, indicating MR imaging demonstrations of relapsed and delayed NiV encephalitis, have obvious differences from those of early NiV encephalitis (Figs. 24.7 and 24.8).

Case Study 1
A male patient aged 44 years.

Acute NiV encephalitis. FLAIR sequence demonstrates multiple lesions in subcortical deep white matter and in deep white matter surrounding the lateral ventricles. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 2
A male patient aged 53 years.

Acute NiV encephalitis. FLAIR sequence demonstrates disseminated round lesions in the white matter of bilateral semioval centers. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 3
A male patient aged 26 years.

Early NiV encephalitis. FLAIR sequence demonstrates subcortical lesions in bilateral semioval centers, and some lesions are in strip-like shape (indicated by black arrows) in the early stage of NiV encephalitis. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 4
A male patient aged 45 years.

Acute NiV encephalitis. FLAIR sequence demonstrates lesions in the gray matter of bilateral semioval centers (indicated by black arrows). For case detail and figures, please refer to Sarji et al. (2000).

Case Study 5
A female patient aged 40 years.

Acute NiV encephalitis (in the late stage). (**a**, **b**) MR imaging demonstrates multiple scattering round-like infarct lesions in bilateral semioval centers. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 6
A male patient aged 40 years.

Acute NiV encephalitis. FLAIR sequence demonstrates fused lesions in the right temporal lobe. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 7
A male patient aged 28 years.

Relapsed NiV encephalitis.(**a**, **b**) FLAIR sequence demonstrates fused lesions in the cortex of parietal lobes and temporal lobes. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 8
Relapsed NiV encephalitis.

(**a**, **b**) Transverse and coronal FLAIR sequences demonstrate extensive involvement of the gray matter. For case detail and figures, please refer to Sarji et al. (2000).

Case Study 9
A female patient aged 31 years.

For case detail and figures, please refer to Sarji et al. (2000).

24.7.3 Pulmonary Lesions

Chest X-ray demonstrates shadows of mild interstitial inflammation in the lungs. There are coarse pulmonary markings, which extend to lung periphery and no large flakes of blurry shadows. The demonstrations are similar to those in patients with atypical pneumonia. The heart shadow is slightly enlarged.

24.8 Diagnostic Basis

The diagnosis of NiV encephalitis requires combination to epidemiological history.

24.8.1 Epidemiological History

The patients are from epidemic area of the disease. And the patients have a history of close contact to pigs or patients with NiV infection 2 weeks prior to the onset. Otherwise, the patients have a history of eating foods possibly contaminated by fruit bats.

24.8.2 Clinical Symptoms

The patients experience symptoms of fever, headache, dizziness, vomiting, different levels of confusion, and obvious brain stem dysfunction.

24.8.3 Laboratory Tests

By immunological assays, NiV-specific antibodies IgM and IgG are detected. Otherwise, by RT-PCR amplification, the virus RNA is detected.

24.8.4 Imaging Demonstrations

In acute and late stages, MR imaging demonstrates multiple small focal lesions in subcortical areas and in the deep white matter; T_2WI and FLAIR demonstrate high signal. MR imaging demonstrates relapsed and delayed encephalitis as consecutive cortical lesions.

24.9 Differential Diagnosis

The imaging demonstrations of NiV encephalitis are various, which should be differentiated from other viral encephalitis, cerebral infarction, and multiple sclerosis.

24.9.1 Herpes Simplex Virus Encephalitis

Herpes simplex virus encephalitis is the most common viral infectious disease of the CNS. In early stage, CT scanning may demonstrate no abnormalities and demonstrates abnormalities after 5–6 days. The lesions are bilateral and multiple, commonly involving the temporal lobe, frontal lobe, insular lobe, and limbic system, especially the bottom of the temporal lobe, orbital surface of the frontal lobe, and hippocampus. The cortex and medulla are concurrently involved, mostly medulla but rarely lenticular nucleus. Plain CT scanning demonstrates flakes of lesions in low and uneven density and inner small flakes of lower density area with irregular boundaries. MRI T_1WI demonstrates lesions in equal and low signal, swelling of adjacent gyrus, and flattened sulcus; T_2WI demonstrates high and uneven signal with irregular boundaries. The lesions may be accompanied by singular or multiple hemorrhage lesions, which are demonstrated as strips or spots of shadows with high density by CT scanning. Their MR imaging signals change along with the development of hematoma. By contrast imaging, the early lesions have no obvious enhancement, and obvious enhancement can be found at week 2–4 of the disease course, which is mainly patches and gyrus-like enhancement. The lesions may have certain space-occupying effect.

24.9.2 Epidemic Encephalitis

Epidemic encephalitis, also known as Japanese encephalitis, is an acute infectious disease of the central nervous system caused by epidemic encephalitis virus. The disease prevails in children, with pandemic and seasonal occurrence. MRI T_1WI shows low or mixed signal lesions in the midbrain, thalamus, and basal ganglia; T_2WI and FLAIR show high signal of the lesions.

24.9.3 Multiple Sclerosis

Multiple sclerosis is the most common demyelinating disease characterized by disseminated multiple lesions and alternative remission and relapse. It commonly occurs in middle-aged and young women. Brain lesions are commonly found in the periventricular areas and deep white matter of the cerebral hemispheres, which are also found in the brain stem and cerebellum. Most lesions are patchy and round like, with fusion of some lesions. Plain CT scanning shows lesions in equal or low density with poorly defined boundaries, multiple lesions in different sizes in most cases, and mostly no significant space-occupying effect. Contrast scanning in the acute or active stage demonstrates ring shape or nodular enhancement of lesions, while no enhancement in the chronic

or after hormone therapy stage. MR imaging shows varying demonstrations of the lesions during different stages of multiple sclerosis. In active stage, T1WI shows low signal and T2WI high signal; DWI is also high signal. In the stationary stage, T1WI demonstrates no obvious lesions, T2WI slightly higher signal, and DWI equal or low signal of the lesions. Contrast imaging demonstrates enhancement of most lesions in the active stage, while no or slight enhancement of lesions in the stationary or after hormone therapy stage. The enhanced lesions morphologically vary, which can be nodular, patchy, circular, semicircular, and arched. The range and strength of enhancement are related to damages of blood–brain barrier and its repair responses. Circular enhancement of the lesions commonly indicates reactivated old lesions, while nodular enhancement indicates newly emerging lesions.

Further Reading

Chua KB, Bellini WJ, Rota PA, et al. Nipah virus: a recently emergent deadly paramyxovirus. Science. 2000;288(5470):1432–5.

Hsu VP, Hossain MJ, Parashar UD, et al. Nipah virus encephalitis reemergence, Bangladesh. Emerg Infect Dis. 2004;10(12):2082–7.

Lim CC, Lee WL, Leo YS, et al. Late clinical and magnetic resonance imaging follow up of Nipah virus infection. J Neurol Neurosurg Psychiatry. 2003;74(1):131–3.

Lo MK, Lowe L, Hummel KB, Sazzad HM, et al. Characterization of Nipah virus from outbreaks in Bangladesh, 2008–2010. Emerg Infect Dis. 2012;18(2):248–55.

Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah virus. Clin Infect Dis. 2009;49(11):1743–8.

Negrete OA, Levroney EL, Aguilar HC, et al. EphrinB2 is the entry receptor for Nipah virus, an emergent deadly paramyxovirus. Nature. 2005;436(7049):401–5.

Ng BY, Lim CC, Yeoh A. Neuropsychiatric sequelae of Nipah virus encephalitis. J Neuropsychiatry Clin Neurosci. 2004;16(6):500–4.

Sarji SA, Abdullah BJ, Goh KJ, et al. MR imaging features of Nipah encephalitis. AJR Am J Roentgenol. 2000;175(2):437–42.

Sazzad HM, Hossain MJ, Gurley ES, et al. Nipah virus infection outbreak with nosocomial and corpse-to-human transmission, Bangladesh. Emerg Infect Dis. 2013;19(2):210–7.