Neurology Asia 2009; 14 : 49 – 52

MR imaging in Nipah virus infection

CC Tchoyoson Lim

Department of Neuroradiology, National Neuroscience Institute, Singapore

Abstract

Advanced diffusion weighted (DW) MRI of the brain in the fatal outbreak of Nipah viral encephalitis among pig workers in Malaysia and Singapore revealed a pattern similar to ischaemic infarction caused by obstruction of small cerebral blood vessels. However, relapse and late-onset cases in Malaysia, and other outbreaks of Nipah virus in Bangladesh and the Hendra virus infection in Australia, showed a different MRI pattern of predominantly confluent cortical lesions. MRI was useful in characterizing the disease in acute infection, as well as detection of spine abnormalities and subclinical infection.

INTRODUCTION

In 1998–1999, the Nipah virus was responsible for a catastrophic outbreak of viral encephalitis among workers in Malaysian pig farms.[1-6] In neighbouring Singapore, which imported live pigs from Malaysia, a cluster of cases occurred among workers at a slaughterhouse.[7-13] The brain MRI features of this novel virus in Singapore patients were different from many of the common viruses that cause viral encephalitis. This review summarises the characteristic neuroimaging features of this novel virus and highlights the similarities and differences from other outbreaks of Nipah virus in Bangladesh and the Hendra virus in Australia.

MRI FEATURES OF ACUTE NIPAH ENCEPHALITIS

In the Singapore outbreak, all patients had multiple small (less than 1 cm in maximum diameter) bilateral abnormalities within the subcortical and deep white matter; in some patients, the cortex, brainstem, and corpus callosum were also involved. The outbreak was initially thought to be caused by Japanese encephalitis[7-10], but the MRI pattern was distinctly different from the characteristic features of bilateral thalamic and basal ganglia involvement typical of Japanese encephalitis.[14,15] Recognition of the MRI pattern may be useful in differentiating the two viral encephalitides, particularly at the height of an epidemic before serologic confirmation is available.

Many of these lesions were detected on diffusion-weighted (DW) MRI, which was advantageous in increasing lesion conspicuity (Figure 1), as well as providing additional information and characterising pathological processes in the brain. DW MRI is capable of depicting acute cytotoxic oedema in the clinical assessment of acute cerebral infarction.[16] In Nipah virus patients with acute infection, DW MRI, supported by contrast enhancement, was helpful in confirming that the effects of acute viral infection were responsible for these lesions, and that they were not pre-existing abnormalities caused by ageing or other non-virus related causes.[7,10]

FOLLOW UP MRI AND FEATURES IN ASYMPTOMATIC PIG WORKERS

On follow up DW MRI in Singapore patients, there was decreased prominence or disappearance of lesions over time, and the appearance of multiple transient hyperintensities on T1-weighted images, primarily in the cerebral cortex. These lesions appeared similar to laminar cortical necrosis and provided further clues to the pathogenesis.[11] Although some patients had persistent or new clinical symptoms such as cranial nerve palsy, depression, personality changes, chronic fatigue syndrome and neuropsychological deficits in attention, verbal and visual memory, surveillance with serial brain MRI over 18 months did not reveal new brain lesions. One patient presented with delayed onset Horner syndrome and a single lesion in the cervical spinal cord was detected on MRI.[12]

Among a group of asymptomatic but seropositive abattoir workers, who were exposed to infected pigs but did not present with encephalitis during the outbreak, delayed MRI revealed discrete small lesions in the brain; similar to those detected in encephalitis patients. These

Address correspondence to: Dr Tchoyoson Lim, Department of Neuroradiology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore, 308433.

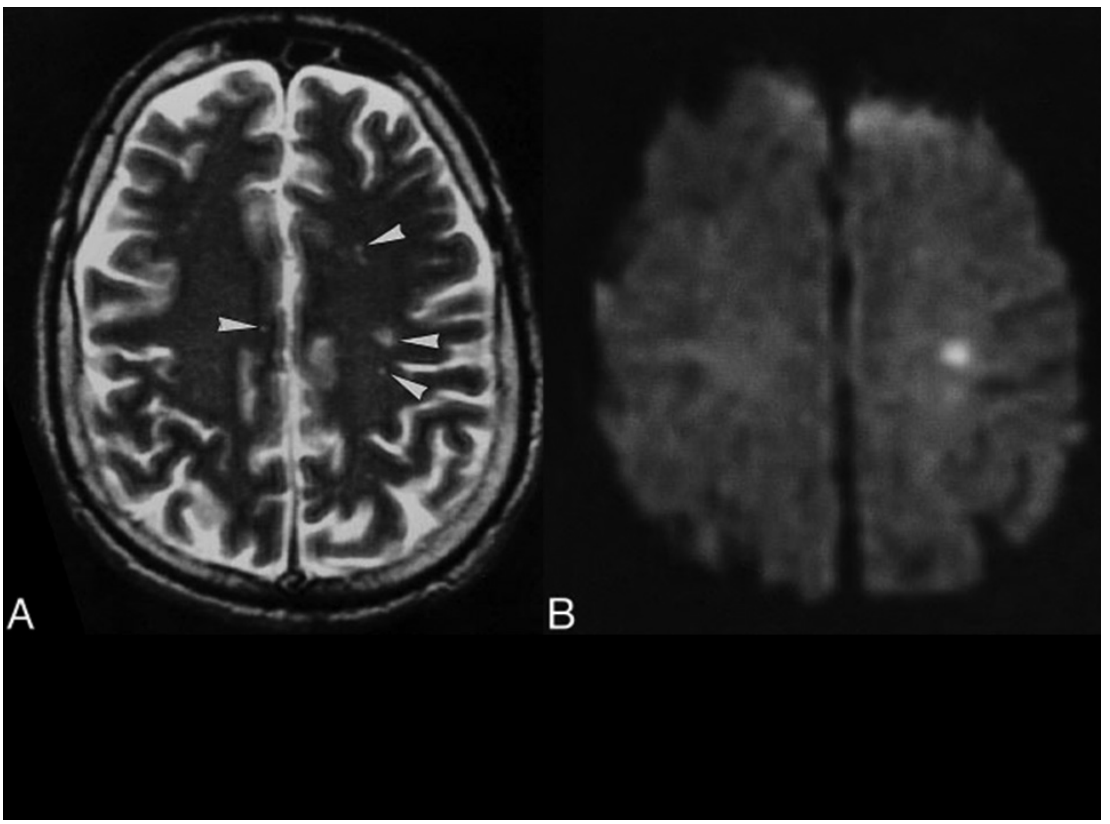

Figure 1. Typical MRI pattern of multiple small white matter lesions

(**A**) Multiple punctate white matter lesions (arrowheads) are visible on T2-weighted MR image. (**B**) The largest lesion is more prominent on corresponding diffusion-weighted image (DWI). (Reprinted with permission from Lim CCT, Sitoh YY, Hui F, *et al*. Nipah viral encephalitis or Japanese encephalitis? - MR findings in a new zoonotic disease. *Am J Neuroradiol* 2000; 21(3):455-61.)

findings suggest that the Nipah virus can cause these lesions, even in subclinical infection.[12]

EVIDENCE FOR MICROANGIOPATHY

The scattered small brain lesions seen on MRI primarily in the white matter in the acute stage were different from most viral encephalitides, and were more reminiscent of common diseases such as embolic cerebral infarction or multiple sclerosis rather than herpes or Japanese encephalitis.[14,15,17,18] The acute abnormalities on DW MRI, the changes and disappearance over time of these lesions and the transient appearance of lesions on T1-weighted images were more consistent with cerebral infarction than demyelination, and similar to other causes of microangiopathy.[19,20] Evidence from the retinal arteries study[12] and histopathology support virus-associated cerebral infarction: autopsy studies of humans suggested that the primary pathology was a multi-organ vasculitis associated with infection of endothelial cells, causing diffuse vasculitis in the cerebral cortex and brainstem with extensive lytic necrosis.[2,3,5] Hence, Nipah virus may cause unique MRI features probably related to vascular damage and ischaemia, unlike those of other viral encephalitides.

Although the most of the MRI findings in the Singapore outbreak could be explained by small focal infarction, other features like hippocampal lesions and the lack of brainstem and cerebellar abnormalities to account for significant clinical deficits still leaves many questions unanswered.[4,6-10]

MRI FEATURES IN OTHER CASES OF NIPAH AND HENDRA VIRUS ENCEPHALITIS

In the Malaysian outbreak, MRI revealed a similar pattern that could be explained by widespread microinfarction from vasculitis but also additional features, suggesting a different pattern. In addition to extensive focal small discrete lesions in the subcortical white matter

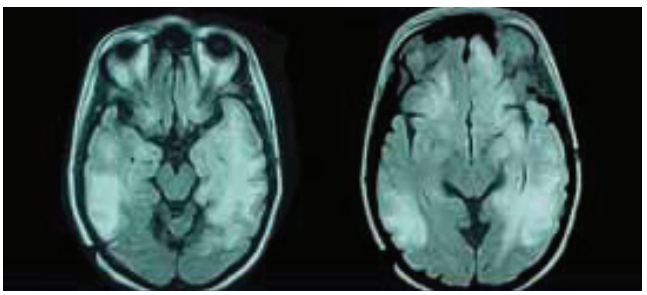

Figure 2. Typical MRI pattern of confluent cortical lesions

Axial fluid attenuated inversion recovery MR image showing multiple confluent lesions in the white matter both temporal, frontal and parietal lobes. There are also involvement of the gray matter in left insular, both frontal, and right parietal lobes. (Reprinted with permission from Quddus R, Alam S, Majumdar MA, *et al*. A report of 4 patients with Nipah encephalitis from Rajbari district, Bangladesh in the January 2004 outbreak. *Neurol Asia* 2004; 9:33-7.)

of the cerebral hemispheres, there was more extensive involvement of the cortex, temporal lobe and pons compared to those seen in Singapore. There were also unique Nipah virus patients who presented with neurologic relapse and late onset encephalitis, and these patients had a different MRI pattern of brain disease, with multiple areas of patchy and confluent cortical involvement.[6] It has been suggested that these lesions may represent a different pathologic mechanism from acute vasculitis-induced microinfarction, with necropsy showing focal encephalitis, consistent with a comparatively greater degree of irreversible neuronal damage in relapsed and late-onset encephalitis.[21,22]

Since the initial discovery of the Nipah virus in the Malaysia-Singapore epidemic of 1998-99, it has re-emerged in Bangladesh in multiple, smaller outbreaks.[23-27] The MRI features of these patients show disseminated multifocal lesions and confluent lesions in both gray and white matter in acute encephalitis (Figure 2).[25,26]

The Nipah virus shares many similarities with the Hendra virus, which is another newly isolated member of the *Paramyxoviridae* family causing zoonotic disease in humans and horses in Australia[28,29]; together they are classified as members of the new genus Henipavirus, which are Biosafety Level 4 pathogens.[30] In the only published MRI of a fatal case of Hendra virus encephalitis[29], widespread cortical lesions were reported, similar in appearance to the late-onset pattern and persistent brain infection of subacute sclerosing panencephalitis caused by measles, the prototypic Paramyxovirus.[31]

RE-EMERGENCE AND THREAT

MRI has been helpful in showing that the henipaviruses can cause different patterns including acute vasculitis-associated cerebral infarction and relapsed and late-onset encephalitis, probably representing different pathological processes. Although it has been 10 years since the initial Malaysian outbreak, the continued re-emergent clusters of Bangladeshi Nipah cases, re-emergence of Hendra virus infection in Australia[32], as well as the remote possibility of using bat-borne zoonotic viruses as biological weapons, means that clinicians need to be aware and vigilant to counter the potential threat from these dangerous pathogens.[33]

In conclusion, the Nipah virus causes different characteristic patterns of MRI features, including widespread small white matter lesions related to cerebral infarction from viral vascular damage. Another distinct group of relapsed and late-onset encephalitis patients had predominantly confluent cortical lesions. During an outbreak, MRI, especially DW MRI, was helpful in characterizing the disease, detection of subclinical infection and demonstrating relapsed and late-onset encephalitis.

REFERENCES

1. Centers for Disease Control and Prevention. Outbreak of Hendra-like virus–Malaysia and Singapore, 1998–1999. *Morb Mortal Wkly Rep* 1999; 48: 265–9.
2. Chua KB, Goh KJ, Wong KT, *et al*. Fatal encephalitis due to Nipah virus among pig farmers in Malaysia. *Lancet* 1999; 354:1257-59.
3. Chua KB, Bellini WJ, Rota PA, *et al*. Nipah virus: a recently emergent deadly paramyxovirus. *Science* 2000; 288:1432-5.

4. Goh KJ, Tan CT, Chew NK, *et al*. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *N Eng J Med* 2000; 342(17):1229-35.
5. Wong KT, Shieh WJ, Kumar S, *et al*. Nipah virus infection: pathology and pathogenesis of an emerging paramyxoviral zoonosis. *Am J Pathol* 2002; 161:2153-67.
6. Ahmad Sarji S, Abdullah BJ, Goh KJ, Tan CT, Wong KT. MR imaging features of Nipah encephalitis. *Am J Roentgenol* 2000; 175:437-42.
7. Lim CCT, Sitoh YY, Lee KE, *et al*. Meningoencephalitis caused by a novel paramyxovirus: An advanced MRI case report in an emerging disease. *Singapore Med J* 1999; 40:356–8.
8. Lee KE, Umapathi T, Tan CB, *et al*. The neurological manifestations of Nipah virus encephalitis, a novel paramyxovirus. *Ann Neurol* 1999; 46:428–32.
9. Paton NI, Leo YS, Zaki SR, *et al*. Outbreak of Nipah virus infection among abattoir workers in Singapore. *Lancet* 1999; 354:1253-6.
10. Lim CCT, Sitoh YY, Hui F, *et al*. Nipah viral encephalitis or Japanese encephalitis? - MR findings in a new zoonotic disease. *Am J Neuroradiol* 2000; 21(3):455-61.
11. Lim CCT, Lee KE, Lee WL, *et al*. Nipah virus encephalitis: Serial MR study in an emerging disease. *Radiology* 2002; 222(1):219-26.
12. Lim CCT, 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.
13. Ng BY, Lim CCT, Yeoh A, Lee WL. Neuropsychiatric sequelae of Nipah virus encephalitis. *Journal of Neuropsychiatry and Clinical Neurosciences* 2004; 16 (4):500-4.
14. Abe T, Kojima K, Shoji H, *et al*. Japanese encephalitis. *J Magn Reson Imaging* 1998; 8:755–61.
15. Kalita J, Misra UK. Comparison of CT scan and MRI findings in the diagnosis of Japanese encephalitis. *J Neurol Sci* 2000; 174:3-8.
16. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. *Radiology* 2000; 217 (2):331-45.
17. Jaeger HJ, Mathias KD, Hauth E, *et al*. Cerebral ischaemia detected with diffusion-weighted MR imaging after stent implantation in the carotid artery. *Am J Neuroradiol* 2002; 23:200-7.
18. Kang DW, Chu K, Ko SB, Kwon SJ, Yoon BW, Roh JK. Lesion patterns and mechanism of ischaemia in internal carotid artery disease: a diffusion-weighted imaging study. *Arch Neurol* 2002; 59:1577-82.
19. Susac JO, Murtagh FR, Egan RA, *et al*. MRI findings in Susac's syndrome. *Neurology* 2003; 61:1783-7.
20. Xu MS, Tan CB, Umapathi T, Lim CC. Susac syndrome: serial diffusion-weighted MR imaging. *Magn Reson Imaging* 2004; 22(9):1295-8.
21. Tan CT, Goh KJ, Wong KT, *et al*. Relapsed and late-onset Nipah encephalitis. *Ann Neurol* 2002; 51:703-8.
22. Chong HT, Tan CT. Relapsed and late-onset Nipah encephalitis: a report of three cases. *Neurol. J. Southeast Asia* 2003; 8:109-12.
23. ICDDRB. Outbreaks of encephalitis due to Nipah/Hendra-like viruses, Western Bangladesh. *Health and Science Bulletin* 2003; 1(5):1-6.
24. Hsu VP, Hossain MJ, Parashar UD, *et al*. Nipah virus encephalitis re-emergence, Bangladesh. *Emerg Inf Dis* 2004; 10(12):2082-7.
25. Quddus R, Alam S, Majumdar MA, *et al*. A report of 4 patients with Nipah encephalitis from Rajbari district, Bangladesh in the January 2004 outbreak. *Neurol Asia* 2004; 9:33-7.
26. Sejvar JJ, Jahangir Hossain, Kama Saha S, *et al*. Long-term neurological and functional outcome in Nipah virus infection. *Ann Neurol* 2007; 62:235-42.
27. Hossain MJ, Gurley ES, Montgomery JM, *et al*. Clinical presentation of Nipah virus infection in Bangladesh. *CID* 2008; 46:977-84.
28. Murray K, Selleck P, Hooper P, et al. A morbillivirus that caused fatal disease in horses and humans. *Science* 1995; 268: 94–7.
29. O'Sullivan JD, Allworth AM, Paterson DL, *et al*. Fatal encephalitis due to novel paramyxovirus transmitted from horses. *Lancet* 1997; 349: 93–5.
30. Eaton BT, Broder CC, Middleton D, Wang LF. Hendra and Nipah viruses: different dangerous. *Nat Rev Microbiol* 2006; 4 (1): 23-35.
31. Ozturk A, Gurses C, Baykan B, Gokyigit A, Eraksoy M. Subacute sclerosing panencephalitis: clinical and magnetic resonance imaging evaluation of 36 patients. *J Child Neurol* 2002; 17:25-9.
32. Hanna JN, McBride WJ, Brookes DL, *et al*. Hendra virus infection in a veterinarian. *Med J Aust* 2006; 185(10):562-4.
33. Ketai L, Lim CCT. Radiology of biological weapons-old and the new? *Seminars in Roentgenology* 2007; 42: 49-59.