

# A Case Report of Japanese Encephalitis Focusing on MR Findings

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## Abstract-

Japanese encephalitis virus (JEV) infection can manifest with nonspecific febrile illness, aseptic meningitis or encephalitis with or without neurological deficits. JEV typically attacks the thalamus, corpus striatum, brainstem and spinal cord. The laboratory diagnosis of JEV infection involves the detection of anti-JEV antibody IgMs using an enzyme-linked immunosorbent assay (ELISA), which has high sensitivity and specificity. Because of the lack of a specific antiviral therapy, JE is usually managed by symptomatic treatment and supportive care. We report a case of JE in a 34-year-old man. With a clinical presentation similar to herpes simplex virus encephalitis, the patient was finally diagnosed as having JE. The distinction of different viral encephalitides in MR findings is briefly reviewed.

**Key Words:** Japanese encephalitis virus, herpes simplex virus, viral encephalitis

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## CASE REPORT

A 34-year-old alcoholic male mechanic was brought to the emergency department (ED) because of consciousness disturbances. The last time when his family contacted him without any type of abnormality was two days prior to admission. His family found him in a confused state with incoherent speech, fever, and urinary and stool incontinence. Upon examination at the ED, his Glasgow coma scale was E4V1M4, and he had bilateral symmetric pupil size with preserved light reflex. Brain computed tomography (CT) showed no evidence of intracranial hemorrhage, cerebral edema or abnormal mass effect. Neck stiffness and Kernig's sign were detected

upon physical and neurological examination. Therefore, a lumbar puncture and cerebrospinal fluid (CSF) study was performed, revealing that the open pressure was 17 cm-CSF, with a reddish appearance. The CSF routine analysis showed a red blood cell (RBC) count of 2600/ $\mu$ L and white blood cell (WBC) count of 250/uL with lymphocyte predominance (73%). The CSF glucose level was 65 mg/dL, and the protein level was 116.5 mg/dL. Subsequent magnetic resonance imaging (MRI) of the brain revealed abnormal T2 hyperintense lesions in the bilateral thalami, putamina, midbrain and pons as well as diffuse gyral swelling involving the bilateral insula, bilateral temporal lobes, and bilateral medial frontal lobes (Figure 1). Herpes simplex virus (HSV) encephalitis was suspected at first,

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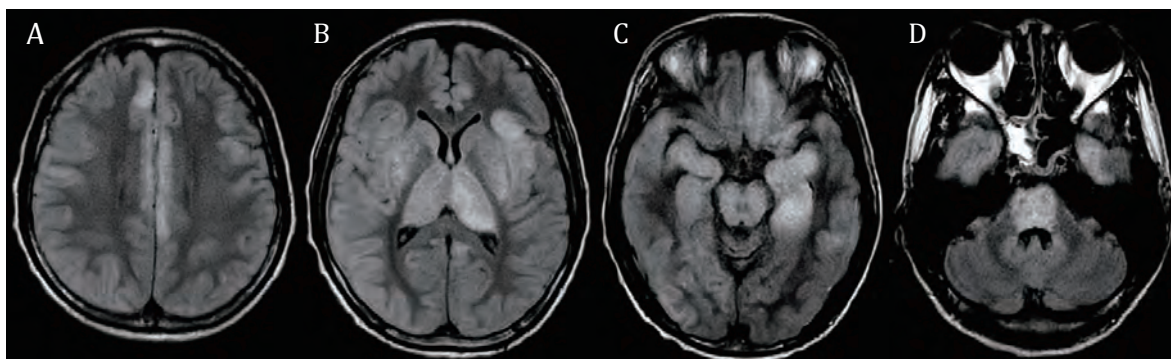
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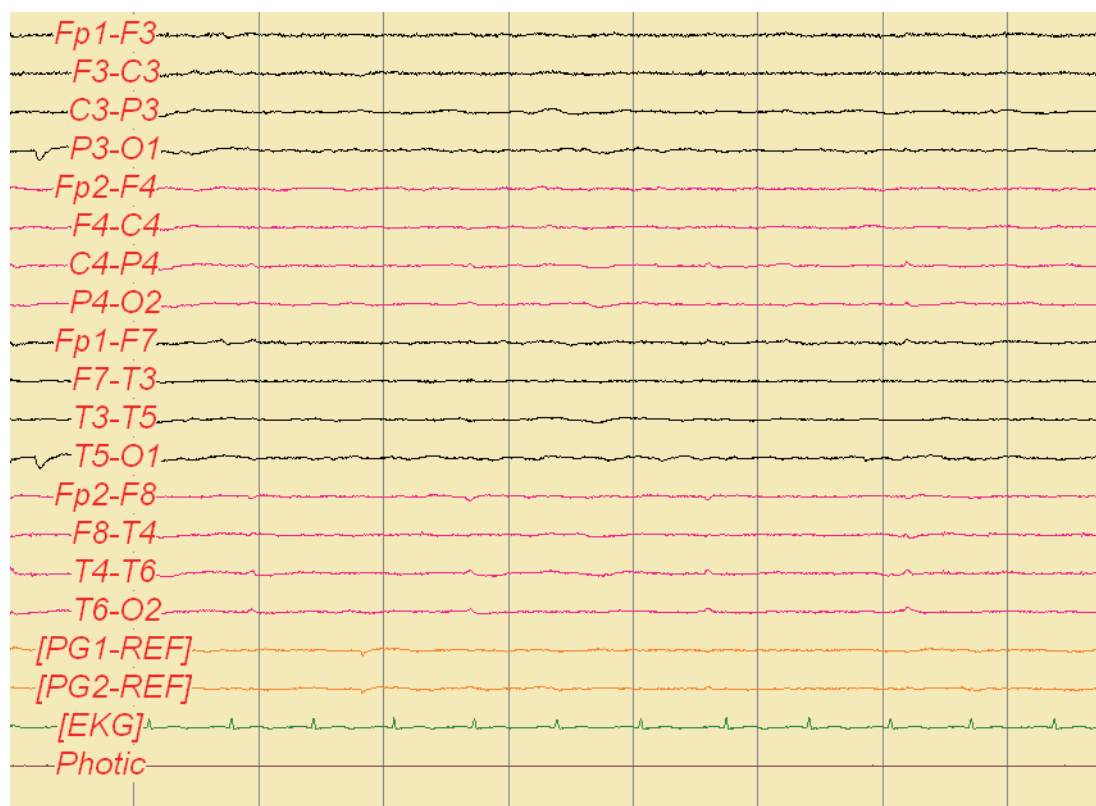
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**Figure 1.** Magnetic resonance imaging (MRI) of the brain revealed abnormal T2 FLAIR hyperintense lesions in the bilateral thalami, putamina (B), midbrain (C) and pons (D) as well as increased signal intensity and gyral swelling involving the bilateral insula (B), bilateral temporal lobes (B,C), and bilateral medial frontal lobes (A).



**Figure 2.** The EEG was performed while the patient was comatose. The background consisted of low-amplitude cortical activities, indicating severe cortical dysfunction.

and antiviral treatment was given immediately. Two days later, the patient lost his light reflex, gag reflex, corneal reflex, and oculocephalic reflex and developed flaccid paralysis in all limbs. Electroencephalography showed

hardly any cortical activity and was concluded to have severe cortical dysfunction (Figure 2). The CSF HSV antibody test for both IgG and IgM was negative, and the patient responded poorly to our empirical antiviral

treatment. Under the suspicion of JE, we contacted the Centers for Disease Control, R.O.C. (Taiwan) for help, and JE was finally diagnosed through the detection of JEV antibodies (both IgG and IgM) in both serum and CSF. Unfortunately, the patient expired 5 days after the diagnosis was made, even under intensive care.

## DISCUSSION

Viral encephalitis is a worldwide health problem due to its extremely high mortality rate. JEV is a single-stranded positive sense RNA virus that belongs to the flaviviridae family. JEV is transmitted through a zoonotic cycle among mosquitoes, pigs and water birds<sup>(1)</sup>. Currently, JE is one of the most important viral and prevalent encephalitides, particularly in Eastern and Southeastern Asia. JE affects more than 50,000 patients worldwide and results in 15,000 deaths annually. In 2013, 16 cases were reported from May to July in Taiwan. Over the last ten years, a total of 296 cases were reported, mostly in the southern part of Taiwan. With the help of early childhood vaccination since 1968, the prevalence of JE has decreased gradually from 7.66/100,000 to 2.04/100,000.

Most of the patients with JEV infection only present with a nonspecific fever, flu-like illness, nausea, anorexia, vomiting and abdominal pain. However, the clinical manifestations vary from nonspecific febrile illness to aseptic meningitis to severe encephalitis. After 6-18 days of infection, symptoms of central nervous system involvement, such as irritability and agitation, personality changes, seizures, and neurological deficits in the form of hemiplegia, quadriplegia or cerebellar dysfunction and/or movement disorders may occur<sup>(2)</sup>. Fewer than 1% of JEV infections result in symptomatic neuroinvasive disease. When neurological symptoms occur, they are usually associated with a high mortality rate. A report from India stated that 20-40% of patients with JE may die during the acute stage<sup>(3)</sup>. Among the survivors, severe neurological sequelae are common. At present, there is no effective management for JE, and the treatment is supportive and symptomatic care. Therefore, the primary prevention of JE is an important public health issue, and it can be achieved by effective vaccination<sup>(4)</sup> and vector control. However, JE remains a life-threatening CNS infection. Physicians, particularly neurologists and infection specialists, need

to be familiar with the clinical manifestations and image findings of this fatal disease.

The typical CT findings in JE are hypodensity in the thalamus and basal ganglia with or without hemorrhaging. MRI reveals abnormal signals in the thalamus, basal ganglia, substantia nigra, cerebellum, pons, cerebral cortex and spinal cord. These MRI lesions are generally hypointense on T1 and hyperintense on both T2 and fluid attenuation inversion recovery (FLAIR) sequences. The thalamic lesions may be of mixed intensity on T1-weighted image (T1WI) and T2-weighted image (T2WI) in the subacute stage, potentially suggestive of hemorrhagic changes. A very important image finding of JE is that the lesion usually first involves the posterior thalamus. It then progresses to the whole thalamus and basal ganglion. Encephalitis with bilateral thalamic involvement should be highly suspicious of JE, but other possibilities, such as HSV, variant Creutzfeldt-Jakob Disease (vCJD), acute necrotizing encephalopathy, Eastern equine encephalitis, Murray valley encephalitis, and tick-borne encephalitis, should also be considered<sup>(5)</sup>.

HSV encephalitis (HSE) features acute inflammation, congestion, and/or hemorrhaging of the brain. Similar to JE, HSE can present with personality changes, confusion, and disorientation. Seizures and focal neurological deficits such as hemiparesis are common. Most importantly, HSE is one of the few currently treatable viral encephalitides. The prognosis is related to an early and accurate diagnosis and immediate antiviral treatment. HSE results in gray matter dysfunctions, and both anterior and medial temporal and frontal lobes could be involved asymmetrically or symmetrically<sup>(6)</sup>. The identification of HSE is important because it can be treated successfully with antiviral therapy. Additionally, HSE is one of the most common causes of acute focal encephalitis and can be diagnosed by molecular biology methods such as polymerase chain reaction (PCR) assays for the detection of HSV DNA in the CSF. Both HSE and JE have a high mortality rate, but in contrast to HSV, a treatment for JEV is not available. No anti-viral therapy can improve the outcome and prognosis of JE. At least one-third of the survivors have significant neurological sequelae<sup>(7)</sup>. Although a histopathological examination is a helpful tool for the diagnosis of JEV, it is not clinically applicable. The current diagnostic methods for JEV rely on JEV IgM detection by ELISA and JEV

RNA sequence detection by PCR. However, these methods are time-consuming and offer no timely guidance for clinical decisions. Characteristic neuroimaging findings could be key for early differentiation.

Among infectious diseases, JE and vCJD may both involve the thalamus. Typical vCJD is associated with spongiform encephalopathy and usually involves bilateral lesions in the posterior thalamus and dorsomedial thalamic nuclei, which are called the pulvinar sign or hockey stick sign<sup>(8)</sup>. Acute necrotizing encephalopathy was first described in Japan by Mizuguchi and colleagues in 1995<sup>(9)</sup>. This disease affects children and young adults and manifests as acute encephalopathy following 2 to 4 days of respiratory infection. Its neuropathology shows multifocal, symmetric brain lesions affecting the bilateral thalami with localized edema, congestion or hemorrhaging. The cerebral periventricular white matter, brainstem, or cerebellum can also be involved.

The imaging study could be similar in JE and HSE, and both could show temporal lobe involvement. In HSE, a brain CT scan typically reveals hypodense, contrast-enhanced lesions in the antero- and medial temporal and inferior frontal regions, with edema and mass effects. Brain MRI is superior to CT scans in the detection of necrosis in the orbitofrontal and medial temporal lobes and the insula. Necrosis is demonstrated by increased signals within the first 48 hours on T2WI or FLAIR sequences<sup>(11)</sup>. However, the involvement of the posterior hippocampus is common, whereas the anterior temporal lobe and insular are usually spared in JE<sup>(10)</sup>. Compared with JE, thalamic involvement is relatively rare in HSE, and abnormal thalamic signals on MRI should be suggestive of JE. Although our first impression for this case was not correct, early antiviral therapy should still be used before a definite diagnosis is made because HSE is a more treatable disease.

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