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Case Series

Radiology Section

Neuroimaging Manifestations and Clinical Correlates of Japanese Encephalitis: Insights from an MRI Case Series

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ABSTRACT

Japanese Encephalitis (JE) poses a significant public health threat across Asia and the Western Pacific, leading to considerable mortality and morbidity if not promptly diagnosed and treated. This flaviviral infection, transmitted by *Culex* mosquitoes, primarily affects children but can impact individuals of all ages. Prompt diagnosis relies on detecting Japanese Encephalitis Virus (JEV) IgM antibodies in serum or Cerebrospinal Fluid (CSF), alongside characteristic Magnetic Resonance Imaging (MRI) findings. In this MRI case series, three confirmed cases of JE are presented, showcasing the typical neuroimaging manifestations observed in affected individuals. All cases exhibited bilateral thalamic hyperintensities on T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) images, a hallmark feature of JE. Additionally, one patient demonstrated involvement of the substantia nigra and bilateral frontal cortex. The clinical implications of present study findings underscore the importance of considering JE as a differential diagnosis in patients presenting with symptoms of encephalitis, especially when MRI reveals bi-thalamic signal alterations. Early recognition and initiation of appropriate treatment, including antiviral agents, are crucial for improving outcomes and reducing mortality. This study contributes to the existing literature by reinforcing the importance of neuroimaging in diagnosing JE and highlighting the distinct MRI patterns associated with the disease. Recognising these characteristic imaging features can aid clinicians in promptly identifying and managing JE cases, thereby mitigating the associated morbidity and mortality.

Keywords: Bilateral thalamic hyperintensities, Diagnosis, Infectious disease, Magnetic resonance imaging

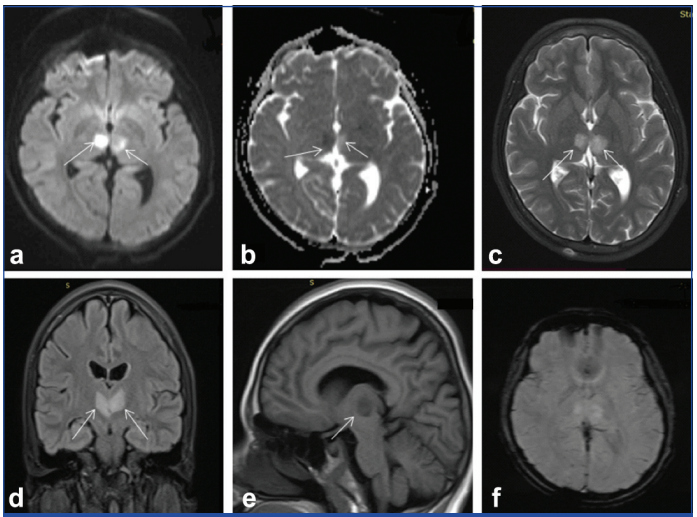
INTRODUCTION

The JE, caused by JEV, is a flavivirus related to dengue, yellow fever, and West Nile viruses, and is the most common preventable cause of mosquito-borne encephalitis in Asia and the Western Pacific. *Culex* species of mosquitoes transmit the virus through their bites. Transmission is most common in agricultural areas such as farms and paddy fields, but can also occur in urban areas [1]. Although most infections are asymptomatic, significant morbidity and mortality are seen in those who develop symptoms of encephalitis. JE is confirmed by CSF or serum IgM ELISA antibody. Typical MRI findings include bilateral thalamic hyperintensities with or without haemorrhage. Other regions like the brainstem, cerebellum, basal ganglia, and cortex may be involved. MRI findings may also be expected in certain patients. Haemorrhage may also be present in the above regions but may not be detectable if imaging is done within the first 3-4 days of the onset of the disease. Co-existing infections with Neurocysticercosis may also be seen [2].

CASE SERIES

Case 1

A 13-year-old boy presented to the emergency department with complaints of two episodes of new-onset seizures, and intermittent low-grade fever for three days associated with vomiting. On examination, vitals were stable, the patient was drowsy, oriented, and able to respond to commands. The rest of the neurological exam was unremarkable. The other system exam was normal. Complete Blood Count (CBC) showed elevated leukocytes. An MRI of the brain [Table/Fig-1a-f] was taken which showed a high Diffusion Weighted Imaging (DWI) signal in bilateral thalami and low Apparent Diffusion Coefficient (ADC) signal in the right thalamus. T2 axial and FLAIR coronal sections showed hyperintense signal of both thalami. No evidence of blooming was noted in Susceptibility Weighted Imaging (SWI) images. Features were consistent with viral encephalitis. The CSF sample showed significantly elevated titres of IgM ELISA antibodies for JE at 1:320. The patient was treated with antipyretics, anticonvulsants, and acyclovir. The patient's general condition improved with no further episodes of seizure.

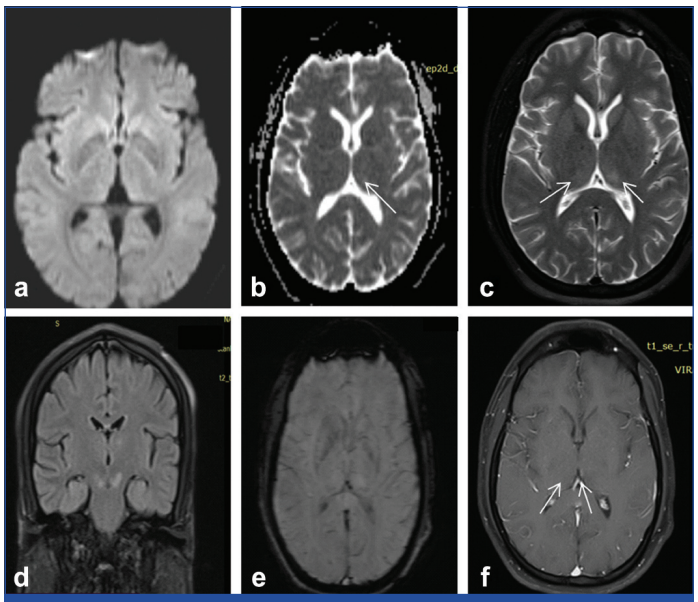


[Table/Fig-1]: Case 1: MRI brain of 13-year-old boy with proven Japanese Encephalitis (JE). a,b) Axial Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) images shows high DWI signal in bilateral thalami (arrows in a) and low Apparent Diffusion Coefficient (ADC) signal in right thalamus (arrow in b); c,d) T2 axial and FLAIR coronal section shows hyperintense signal of both thalami (arrows); e) T1 sagittal images at left thalamus shows hypointense signal (arrow); f) Susceptibility Weighted Imaging (SWI) axial sections at the level of thalami shows no evidence of any blooming.

Case 2

A 33-year-old male presented to the emergency department with complaints of one episode of seizure, headache, and generalised myalgia for five days. On examination, vitals were stable, the patient was conscious, oriented, and able to respond to commands. The rest of the neurological exam was unremarkable. The other system exam was normal. CBC showed leukocytes and mildly elevated RBC counts. An MRI of the brain [Table/Fig-2a-f] was taken to rule out any space-occupying lesions. The MRI showed high DWI

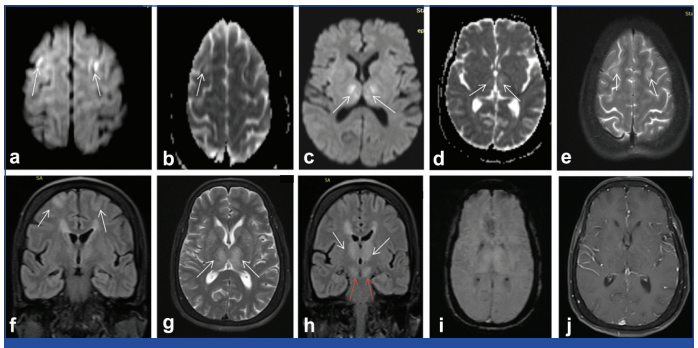
and ADC signal in bilateral thalamus. T2 axial and FLAIR coronal sections show the hyperintense signal of both thalami. No evidence of blooming was noted in SWI images. Features were consistent with viral encephalitis. The CSF sample showed significantly elevated titres of IgM ELISA antibodies for JE at 1:640. The patient was treated with anticonvulsants and acyclovir. The patient's general condition improved with no further episodes of seizure.



[Table/Fig-2]: Case 2: MRI brain of Japanese Encephalitis (JE) in a 33-year-old male. a,b) Axial Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) Images shows subtle high ADC signal in left thalamus (white arrow); c,d) T2 axial and FLAIR coronal shows subtle hyperintense signal of both thalami (arrows) ; e) SWI axial sections at the level of thalami shows no evidence of any blooming; f) T1 C+ FS axial section shows no evidence of any enhancement.

Case 3

A 59-year-old female presented to the emergency department with complaints of high-grade fever associated with a headache, drowsiness, and altered consciousness. On examination, vitals were stable; the patient was drowsy, disoriented, and not able to respond to commands. The rest of the neurological exam was unremarkable. The other system exam was normal. CBC showed elevated leukocytes and anaemia. An MRI of the brain [Table/Fig-3a-j] was taken, which showed high DWI and ADC signal in bilateral thalamus, bilateral substantia nigra, and bilateral middle frontal gyri. T2 axial and FLAIR coronal sections showed hyperintense signal of both thalami, bilateral substantia nigra, and bilateral middle frontal gyri. No evidence of blooming was noted in SWI images. Features were consistent with viral encephalitis. The CSF sample showed significantly elevated titres of IgM ELISA antibodies for JE at 1:1280.



[Table/Fig-3]: Case 3: MRI brain of Japanese Encephalitis (JE) in a 59-year-old female. a,b) Axial Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) images at high frontal level shows high DWI and ADC signal in bilateral middle frontal gyri (arrows); c,d): Axial Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) images at the level of thalami shows high DWI and ADC signal in bilateral thalami (arrows); e,f): Axial T2 and Coronal FLAIR section shows high signal in bilateral middle frontal gyri (arrows) ; g,h): Axial T2 and Coronal FLAIR section high signal intensity in both thalamus (arrows) and substantia nigra (red arrows); i) SWI axial sections at the level of thalami shows no evidence of any blooming; j) T1 C+ PS axial section shows no evidence of any enhancement of the above mentioned regions.

The patient was treated with antipyretics, anticonvulsants, and acyclovir. The patient's general condition improved with no further episodes of seizure.

All patients with serologically proven JE showed abnormal signal alterations in bilateral thalami, which are typical MRI findings described in the literature. One patient showed involvement of the substantia nigra and bilateral frontal cortex. So, if a patient presents with symptoms of encephalitis and if an MRI shows bi-thalamic signal alterations, then JE should be considered as a top differential diagnosis. Clinical presentation, MRI observations, and treatment of three patients are shown in [Table/Fig-4].

Patient	Age (years)/ Gender	Presenting symptoms	MRI findings	Treatment
Case 1	13/M	New-onset seizures, low-grade fever, vomiting	Bilateral thalamic hyperintensity on T2/FLAIR, right thalamic diffusion restriction, no blooming on SWI	Antipyretics, anticonvulsants, acyclovir
Case 2	33/M	Seizure, headache, generalised myalgia	Bilateral thalamic hyperintensity on T2/FLAIR, subtle left thalamic diffusion restriction, no blooming on SWI	Anticonvulsants, acyclovir
Case 3	59/F	High-grade fever, headache, drowsiness, altered consciousness	Bilateral thalamic, substantia nigra, and bilateral middle frontal gyrus hyperintensity on T2/FLAIR, no blooming on SWI	Antipyretics, anticonvulsants, acyclovir

[Table/Fig-4]: Characteristics of three patients: clinical presentation, MRI observations, and treatment.

DISCUSSION

JE presents significant epidemiological variations worldwide, with outbreaks yielding annual incidence rates ranging from under 1 to over 10 cases per 100,000 individuals. An estimated 68,000 clinical cases of JE occur annually, resulting in 13,600 to 20,400 deaths. While predominantly affecting children, individuals of all ages can be impacted, with most adults in endemic areas developing immunity post childhood infection. JEV transmission occurs primarily through *Culex* mosquito bites, notably *Culex tritaeniorhynchus*, maintaining a transmission cycle involving mosquitoes, pigs, and/or water birds in rural and peri-urban areas. Transmission peaks during warmer seasons in temperate regions and during the rainy season and before rice harvest in tropical and subtropical areas [3].

The majority of JEV-infected individuals remain asymptomatic, with less than 1% developing clinical illness, typically characterised by acute encephalitis. Initial symptoms include sudden fever, headache, and vomiting, progressing to potential mental status changes, neurological deficits, weakness, and movement disorders over subsequent days [4]. A characteristic presentation of JE includes symptoms resembling Parkinson's disease, such as a rigid facial expression, tremors, and abnormal movements. Additionally, acute flaccid paralysis, resembling poliomyelitis, has been linked to JE. Seizures, particularly in children, are common. The fatality rate ranges from 20 to 30%, with survivors often experiencing significant neurological, cognitive, or psychiatric issues, affecting 30 to 50% of cases [5].

T2 and FLAIR hyperintensities in typical JE are seen in the thalamus, substantia nigra, basal ganglia, hippocampus, and pons, and less commonly in cortical and subcortical regions and cerebellar hemispheres. DWI can detect cytotoxic oedema, the earliest sign of the encephalitis process. As a result, DWI is more sensitive in JE cases that occur early but less sensitive in situations that occur later. DWI can identify changes in the brain parenchyma of JE patients hours or days before detectable abnormalities show up on T2WI

and FLAIR imaging. Diffusion restriction with low ADC signal is seen in acute cases of JE. ADC values gradually increase after the late acute phase and remain higher in the chronic phase [6].

In present case series, low ADC was observed in one patient involving the right thalamus. The rest of the patients showed high DWI and ADC signal. In the research conducted by Prakash M et al., among the 54 participants, 53 exhibited hyperintensities in both thalamic regions, while bilateral involvement of the substantia nigra was observed in 44 individuals. Lentiform nuclei were affected in 29 patients, and caudate nuclei showed involvement in 8 patients. Hippocampal participation was noted in 14 individuals, with cortical involvement seen in 21 patients. Brainstem inclusion was identified in 8 patients, and microbleeds were present in the thalamus of two patients [7]. In present study, every participant displayed bilateral thalamic involvement, while only one patient exhibited involvement of the substantia nigra and cortex. None of the participants showed microbleeds. In the initial phase of the disease, Keng LT and Chang LY demonstrated a development of T2 and FLAIR hyperintensities in the thalami [8]. As JE advanced, the subacute stage revealed a T2 shrine-through effect in the lesions. Additionally, there was an incremental rise in the ADC value, accompanied by the obscuring of bright signals on DWI.

JE accompanied by Cerebral Venous Sinus Thrombosis (CVST) is an uncommon event, with only a limited number of cases documented in the literature [9]. Distinguishing between dengue encephalitis and JE can be challenging due to their similar imaging characteristics. Both conditions often exhibit hyperintensities on T2 and FLAIR sequences, along with restricted diffusion, particularly evident in the thalami and basal ganglia. In some cases, the involvement can extend to other brain regions such as the pons, medulla, cerebellum, corpus callosum, and cerebral cortex. However, dengue encephalitis tends to present with a higher prevalence of parenchymal or extra-axial bleeding compared to JE. Additionally, diffuse cerebral oedema may occur, and cerebellitis is more commonly observed in dengue encephalitis compared to JE [10].

Other potential diagnosis to consider include cerebral malaria, extrapontine myelinolysis, and deep cerebral venous thrombosis affecting the straight sinus or internal cerebral vein. This condition manifests as hyperintensities in both thalamic regions and the brainstem, with observable areas of blooming [11]. The use of MR Venography and SWI images aids in the identification of thrombosis. In instances of acute thrombosis, the thrombus may exhibit hyperdensity on Computed Tomography (CT) scans. Artery of Percheron infarcts also display bilateral thalamic hyperintensities with diffusion restriction, and clinically, patients may present with vertical gaze palsy [12]. The characteristic “V sign,” a hyperintense signal along the midbrain surface adjacent to the interpeduncular fossa, is classically described and is best visualised on axial FLAIR and DWI images [13].

Wernicke encephalopathy stands out as a crucial consideration in the differential diagnosis due to its clinical features overlapping with encephalitis. MRI findings typically reveal symmetrically increased signal intensity in the mammillary bodies, tectal plate dorsomedial thalami, and periaqueductal grey matter around the third ventricle on T2/FLAIR sequences. Post-gadolinium contrast enhancement may also occur in these regions, with the mammillary bodies being the most commonly affected.

Biochemical assays for vitamin B1 levels in serum may indicate a decrease. Additionally, thalamic glioma represents a noteworthy neoplasm that can mimic the presentation of viral encephalitis [14].

To diagnose JE, the typical laboratory approach involves testing serum or CSF for the presence of virus-specific IgM antibodies. These antibodies are usually identifiable 3 to 8 days after the onset of symptoms and can persist for 30 to 90 days, with instances of even longer persistence documented. However, it’s important to acknowledge that positive IgM antibodies may sometimes indicate a previous infection or vaccination. If serum collected within the first 10 days of illness onset doesn’t reveal detectable IgM, the test should be repeated using a convalescent sample [15].

Confirmatory testing for patients with JE virus IgM antibodies should include neutralising antibody testing. In fatal cases, additional diagnostic approaches like nucleic acid amplification, histopathology with immunohistochemistry, and virus culture from autopsy tissues can provide valuable insights [16].

Treatment for JE involves conservative measures and the use of medications such as minocycline, interferon, ribavirin, immunoglobulin, dexamethasone, and acyclovir. Among these, minocycline has shown promising results in clinical outcomes [17,18].

CONCLUSION(S)

Present study MRI case series emphasises the importance of recognising JE as a differential diagnosis in patients presenting with encephalitis symptoms, particularly when MRI reveals bilateral thalamic hyperintensities. Early identification facilitates prompt treatment initiation, improving patient outcomes. Present study highlights the crucial role of neuroimaging in JE diagnosis and underscores the need for multidisciplinary collaboration for effective management. Confirmation through virus-specific IgM antibody testing is essential for accurate diagnosis. Overall, present study findings stress the significance of timely intervention in JE cases to reduce mortality and morbidity.

Authors contribution: ALR, AH: Concept and design; AH, ALR, and VR: Sourcing and editing of clinical images and investigation results; ALR: Drafting of the manuscript. All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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