



Leptomeningeal Enhancement without Thalamic Involvement as an Initial Manifestation of Japanese Encephalitis: A Case Report

시상 침범 없는 연수막 조영증강을 보인 일본뇌염: 증례 보고

Sang Hwa Woo, MD , Ho-Joon Lee, MD , Yeonah Kang, MD*

Department of Radiology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Japanese encephalitis (JE) is a common infection caused by the Japanese encephalitis virus in Southeast Asia, which is transmitted to humans through *Culex* mosquitoes. Magnetic resonance imaging (MRI) is used to diagnose JE, which is often characterized by the presence of bilateral symmetric thalamic involvement. Here, we report a rare case of JE characterized by leptomeningeal enhancement without thalamic involvement. This leptomeningeal enhancement disappeared with the treatment; however, new non-specific multifocal and bilateral high signal intensities in the cerebral white matter were found on follow-up MRI.

Index terms Japanese Encephalitis; Meningitis; Magnetic Resonance Imaging

INTRODUCTION

Japanese encephalitis (JE) is a common infection in Southeast Asia (1, 2) that is caused by the Japanese encephalitis virus (JEV), a RNA virus that belongs to the Flaviviridae family, which is transmitted to humans via *Culex* mosquitoes (2). Usually, JE infections clinically manifest as a nonspecific febrile illness, ranging from aseptic meningitis to severe encephalitis (2). In some cases, patients develop an encephalitis syndrome that is clinically characterized by altered mental status, seizures, behavioral abnormalities, and movement disorders in the form of parkinsonian features (3).

The clinical diagnosis is confirmed by detecting JE virus-specific immunoglobulin M (IgM) antibodies in the cerebrospinal fluid (CSF) of patients via an enzyme-linked im-

Received May 7, 2020
Revised July 17, 2020
Accepted August 2, 2020

*Corresponding author

Yeonah Kang, MD
Department of Radiology,
Haeundae Paik Hospital,
Inje University College of Medicine,
875 Haeun-daero, Haeundae-gu,
Busan 48108, Korea.

Tel 82-51-797-0381

Fax 82-51-797-0379

E-mail bsb2312@gmail.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Sang Hwa Woo

<https://orcid.org/0000-0002-7869-5514>

Ho-Joon Lee

<https://orcid.org/0000-0003-0831-6184>

Yeonah Kang

<https://orcid.org/0000-0002-5078-3213>

munosorbent assay (ELISA) (1). Magnetic resonance imaging (MRI) has also been used to diagnose JE (1, 4), which is often characterized by the presence of bilateral symmetric thalamic involvement; this is followed by the involvement of the putamen, caudate nucleus, globus pallidus, hippocampus, and substantia nigra (1, 4). However, previous studies have rarely described leptomeningeal involvement in cases of JE.

We report a rare case of JE that manifested with diffuse leptomeningeal enhancement without the definite involvement of the bilateral thalamus on the initial MRI.

CASE REPORT

A previously healthy 54-year-old female presented to our clinic with a headache and neck stiffness, which had lasted for the previous seven days, as well as a moderate fever (38.4°C) that began four days earlier. Furthermore, she was periodically losing consciousness and her orientation of time was deteriorating. She also responded slowly to external stimulus.

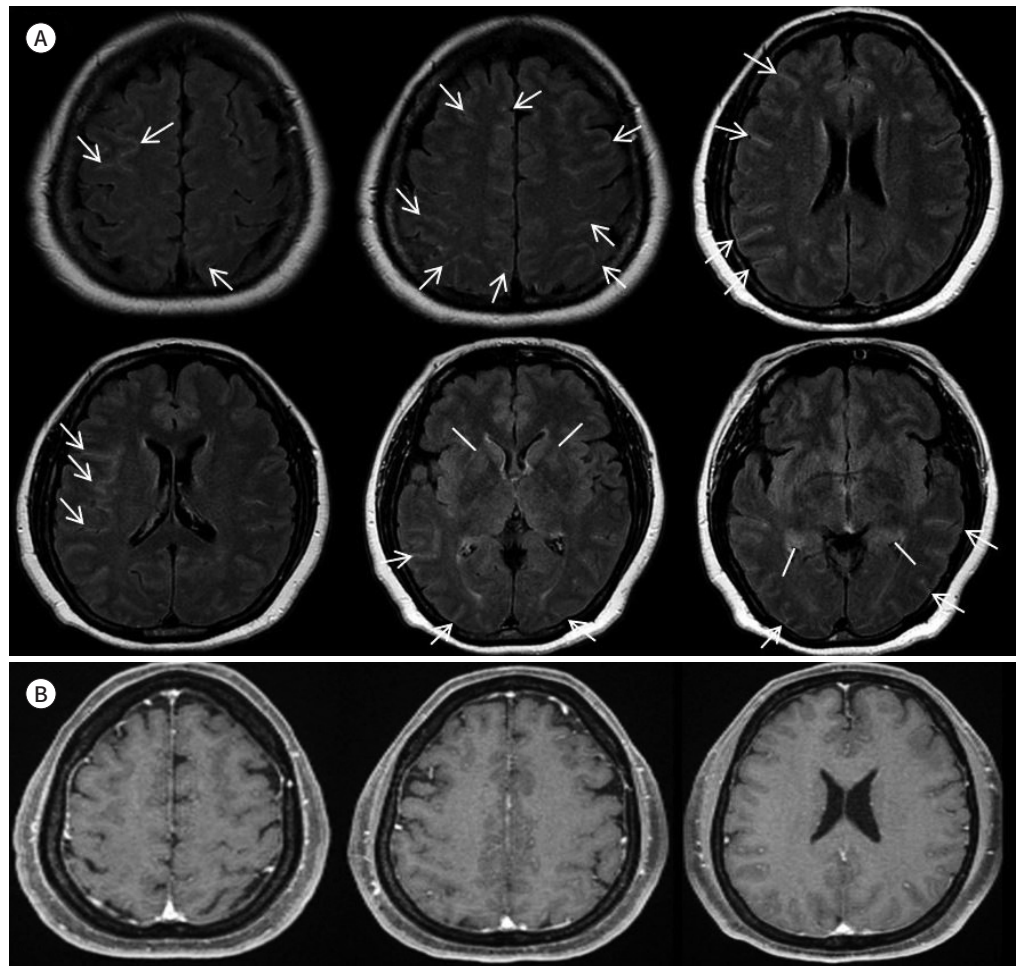
The requirement to obtain informed consent was waived in this study and this study was approved by our hospital's institutional review board (IRB no. 2019-12-019).

The results of the routine hematology and liver function tests were normal. Her C-reactive protein (CRP) level was elevated [6.07 mg/dL (< 0.30 mg/dL)]. On a routine CSF analysis, the patient's white blood cell count [320/mm³ (< 5 cells); lymphocytes 80% (60% ± 20), polymorphonucleocytes 20% (30% ± 15)], glucose level [69 mg/dL (50–75 mg/dL)], and level of protein [134.7 mg/dL (15–45 mg/dL)] were elevated. An initial brain MRI revealed diffuse leptomeningeal enhancement on post-contrast T2 fluid-attenuated inversion recovery (FLAIR) images (Fig. 1A), however, it was not noticeable on post-contrast T1-weighted images (Fig. 1B). Moreover, subtle high FLAIR signal intensities were noted in the bilateral caudate nucleus, putamen and hippocampi. There was no hemorrhage on the gradient echo (GRE) sequences, and no remarkable findings on T1-weighted images. Based on her clinical manifestations and MRI findings, a differential diagnosis of infectious meningoencephalitis was suggested. Initial serological tests yielded negative results for hepatitis B surface antigen, cytomegalovirus, varicella zoster virus, Cryptococcus antigen, tuberculosis, Human T-lymphotrophic viruses I and II, enterovirus, and Herpes simplex viruses I and II. Furthermore, autoantibody tests were normal [IgG of 874.9 mg/dL (700–1600 mg/dL), IgA of 112.1 mg/dL (70–400 mg/dL), and IgM of 122.9 mg/dL (40–230 mg/dL)]. Two days after admission, the patient showed symptoms of Parkinson's disease, including resting tremors involving the whole body, rigidity, and a gait disturbance. Although leptomeningeal involvement is not a typical presentation of JE, MRI findings of the bilateral basal ganglia coupled with the presence of hippocampal involvement indicated the possibility of JE. Therefore, the CSF was analyzed again, which was positive for the presence of JEV-specific IgM. In accordance with the diagnostic criteria described by Burke and Nisalak (5), she was diagnosed with JE.

She received a conservative treatment, which consisted of 24 cc/hr of immunoglobulin intravenously for 5 days and the antiviral drug acyclovir (250 mg/V·2.5 VI) for 2 weeks, in tandem with supportive care to reduce her body temperature. Two weeks after her admission, her CRP levels decreased [0.23 mg/dL (< 0.30 mg/dL)]. Moreover, a follow-up CSF analysis showed decreases in her white blood cell counts [40/mm³ (< 5 cells); lymphocytes 90% (60%

Fig. 1. MRI findings of a 54-year-old female with Japanese encephalitis.

A, B. The initial MRI scans. Diffuse leptomeningeal enhancement (arrows) are noted as high signal intensities in the bilateral frontal, parietal, and insular areas on post-contrast fluid-attenuated inversion recovery images. In addition, subtle high signal intensities are noted in the bilateral caudate nuclei, putamen, and hippocampi (lines). There is no definite involvement of the bilateral thalamus (**A**). However, leptomeningeal enhancement is not noticeable on post-contrast T1-weighted images (**B**).

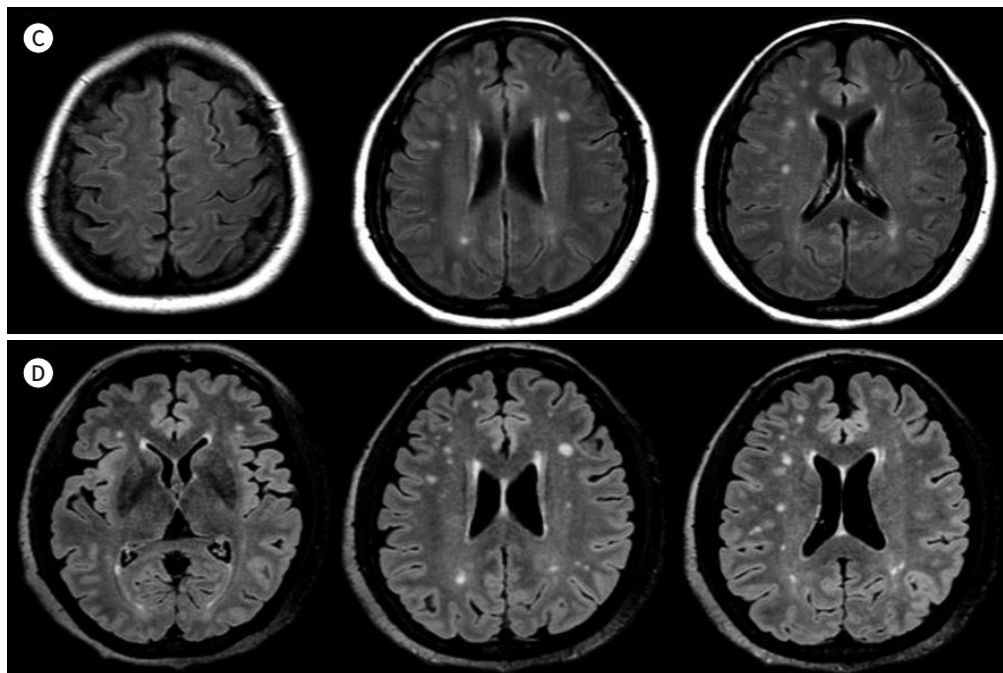


± 20), polymorphonucleocytes 10% ($30\% \pm 15$]), level of glucose [55 mg/dL (50–75 mg/dL)], and protein [112.6 mg/dL (15–45 mg/dL)]. Her mental confusion, headache, cognitive dysfunction, Parkinsonism, and gait disturbance had recovered. Consequently, she was discharged after 18 days of hospitalization. A follow-up MRI, which was obtained on the day of her discharge, demonstrated that the diffuse leptomeningeal enhancement on post-contrast FLAIR imaging had largely resolved. However, new non-specific multifocal and bilateral high signal intensities in the cerebral white matter had developed (Fig. 1C), and the bilateral high signal intensities at the caudate nucleus and hippocampi were still present. When the patient visited an outpatient clinic after discharge, she described having good memory and no functional impairment. In the 8 months post-discharge follow-up MRI, improvement of previous subtle FLAIR high signal intensity in the bilateral basal ganglia and hippocampus was noted; however, multifocal high signal intensities remained in the cerebral white matter (Fig. 1D).

Fig. 1. MRI findings of a 54-year-old female with Japanese encephalitis.

C. The follow-up MRI scan on the day of discharge shows resolved leptomeningeal enhancement and newly developed multifocal high signal intensities in the white matter on post-contrast fluid-attenuated inversion recovery images.

D. These multifocal high signal intensities in the cerebral white matter have persisted on the 8-month post-discharge follow-up MRI scan.



DISCUSSION

Given its sudden onset, JE is a severe illness, with a rapid development of symptoms and a strong risk for morbidity and mortality (1). Therefore, early diagnosis and proper treatment is crucial towards improving the patient's prognosis. We confirmed the diagnosis of JE by detecting JEV-specific antibodies via ELISA (1).

Brain MRI plays a significant role in raising early suspicion of JE. Previous work has suggested that patients with JE typically show MRI aberrations in the thalamus, basal ganglia, substantia nigra, cerebellum, brain stem, medial temporal lobe, and cerebral white matter lesions, which present as high signal intensities in T2-weighted images, and can range from hypo- to iso-signal intensities in T1-weighted images (1, 4, 6). By contrast, the MRI of our patient showed uncommon radiologic findings for JE, and initially presented with diffuse leptomeningeal enhancement without thalamic involvement. Leptomeningeal enhancement manifested as a result of inflammatory cells or substances (e.g., glycoproteins) and a breaking down of the blood-brain barrier without ameliorating angiogenesis. This in turn allows for contrast material to leak from vessels into the CSF (6). Given that JEV invades the central nervous system through hematogenous routes, we speculate the infection of blood cells induced the breakdown of the blood-brain barrier, and by extension, leptomeningeal enhancement.

Currently, very few cases of JE presenting with leptomeningeal enhancement bilaterally in the cerebral hemisphere have been reported. In our case, we observed that leptomeningeal

enhancement was only demonstrated in the post-contrast FLAIR image and not in the three-dimensional (3D) GRE T1-weighted image. This finding may be attributed to the higher sensitivity of FLAIR at low concentrations of gadolinium compared to 3D-GRE T1-weighted images. Our observation is in line with a previous study demonstrating that post-contrast FLAIR provides more valuable information than post-contrast 3D-T1-GRE in leptomeningeal pathology (7). Moreover, to the best of our knowledge, the presentation of meningitis without a thalamic lesion has not been previously described. Thalamic involvement is the most commonly described abnormality in patients with JE. However, while thalamic involvement can be highly specific for JE in the appropriate clinical context, it is not a very sensitive marker of JE (8). A helpful clue for the radiological differential diagnosis of our case was the concurrent involvement of the bilateral caudate nuclei, which is not common within cases of herpes encephalitis.

Eighteen days after admission, the patient's follow-up MRI showed that the extent of bilateral leptomeningeal enhancement had decreased upon post-contrast FLAIR imaging. In addition, at the time of the follow-up MRI, the patient's mental confusion and cognitive dysfunction were completely improved. Meanwhile, the patient had developed new multifocal and non-specific small lesions bilaterally in the cerebral white matter that were observed as high signal intensities in T2-weighted images, which was different from the confluent or patchy white matter changes described in previous study (9). In a pathology study, Shoji et al. (9) suggested that the involvement of white matter may correlate with necrosis or diffuse gliosis as well as a softening of the cerebral white matter. This explanation may be supported by Sarji et al. (10), who reported lesions with high signal intensities in the subcortical and deep cerebral white matter as MRI features of patients with Nipah encephalitis. These lesions with high signal intensities are attributed, via autopsies, to widespread microinfarctions as a result of the vasculitis of small vessels (10). In addition, the observation that MRI findings did not correlate with patient outcomes suggests that the MRI findings reflect widespread micro-infarcts and ischemia (10). Hence, poor patient outcome is probably related to the extent of direct neuronal involvement. Similar to this work, our patient's focal neurological signs did not correlate with the presence of high signal intensities in cerebral white matter in the MRI. Therefore, we speculated that this incongruence can be attributed to the presence of micro-infarctions derived from the vasculitis of small vessels, which occurs because of a hematogenous viral infection.

Given its sudden onset and severe symptoms, JE is a severe infection of great concern. Consequently, early diagnosis and proper treatment is crucial for improving the patient's prognosis. To the best of our knowledge, we documented the first case of a patient with JE who presented with a leptomeningeal enhancement similar to non-specific meningitis without any thalamic involvement. Thus, recognizing atypical radiologic findings of JE may be helpful in the early diagnosis of JE, which may change the prognoses of patients.

Author Contributions

Conceptualization, K.Y., L.H.; data curation, W.S.H.; formal analysis, all authors; investigation, K.Y., W.S.H.; supervision, K.Y.; writing—original draft, W.S.H.; and writing—review & editing, K.Y.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding

None

REFERENCES

1. Mehra S, Garga UC. Role of imaging in herpes and Japanese encephalitis—two cases and review of literature. *J Indian Acad Clin Med* 2012;13:338-343
2. Misra UK, Kalita J. Overview: Japanese encephalitis. *Prog Neurobiol* 2010;91:108-120
3. Misra UK, Kalita J. Prognosis of Japanese encephalitis patients with dystonia compared to those with parkinsonian features only. *Postgrad Med J* 2002;78:238-241
4. Kalita J, Misra UK, Mani VE, Bhoi SK. Can we differentiate between herpes simplex encephalitis and Japanese encephalitis? *J Neurol Sci* 2016;366:110-115
5. Burke DS, Nisalak A. Detection of Japanese encephalitis virus immunoglobulin M antibodies in serum by antibody capture radioimmunoassay. *J Clin Microbiol* 1982;15:353-361
6. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *Radiographics* 2007;27:525-551
7. Fukuoka H, Hirai T, Okuda T, Shigematsu Y, Sasao A, Kimura E, et al. Comparison of the added value of contrast-enhanced 3D fluid-attenuated inversion recovery and magnetization-prepared rapid acquisition of gradient echo sequences in relation to conventional postcontrast T1-weighted images for the evaluation of leptomeningeal diseases at 3T. *AJNR Am J Neuroradiol* 2010;31:868-873
8. Dung NM, Turtle L, Chong WK, Mai NT, Thao TT, Thuy TT, et al. An evaluation of the usefulness of neuroimaging for the diagnosis of Japanese encephalitis. *J Neurol* 2009;256:2052-2060
9. Shoji H, Kida H, Hino H, Matsuura S, Kojima K, Abe T, et al. Magnetic resonance imaging findings in Japanese encephalitis. White matter lesions. *J Neuroimaging* 1994;4:206-211
10. Sarji SA, Abdullah BJ, Goh KJ, Tan CT, Wong KT. MR imaging features of Nipah encephalitis. *AJR Am J Roentgenol* 2000;175:437-442

시상 침범 없는 연수막 조영증강을 보인 일본뇌염: 증례 보고

우상화 · 이호준 · 강연아*

일본뇌염은 동남아시아에서 일본뇌염 바이러스에 의해 발생하는 흔한 감염이며, *Culex* 모기에 의해 인간으로 전파된다. 일본뇌염에서의 자기공명영상은 양측의 시상 침범이 있는 것이 흔한 소견이다. 저자들은 시상 침범 없이 연수막 조영증강의 형태로 나타난 일본뇌염의 드문 증례에 대해 보고하고자 한다. 치료 후, 연수막 조영증강은 사라졌으며, 비특이적인 다발성 및 양측의 고신호강도가 추적 MRI 영상에서 새롭게 나타났다.

인제대학교 의과대학 해운대백병원 영상의학과