

# A Possible Case of Acute Disseminated Encephalomyelitis after Japanese Encephalitis

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## Abstract

**Purpose:** Acute disseminated encephalomyelitis (ADEM) is a monophasic demyelination disease of central nervous system (CNS) with presentations of impaired consciousness, neurologic deficits and diffuse white matter lesions on magnetic resonance imaging (MRI). Predisposing infection can be identified in around 50 to 77% of all patients with ADEM. Post-infectious autoimmune events associated with Japanese encephalitis have been limited to case reports of Guillain-Barre syndrome after Japanese encephalitis and Japanese encephalitis virus vaccine-related ADEM. We herein report the first possible patient with Japanese encephalitis developed a subsequent ADEM after recovery from Japanese encephalitis.

**Case Report:** A 50-year-old man suffered from an acute onset of headache, fever, and disturbance of consciousness. Japanese encephalitis was diagnosed by virological and image study. He recovered gradually and was discharged about 1.5 months later. However, another episode of consciousness impairment with violent behavior occurred 21 days after discharge. Acute disseminated encephalomyelitis was confirmed by brain MRI which showed newly developed diffuse white matter lesions. His clinical symptoms and abnormal brain lesions on MRI improved gradually after combination of high-dose intravenous methylprednisolone and oral steroid therapy.

**Conclusion:** Our patient is a possible case of ADEM developing after Japanese encephalitis. High dose steroid therapy resulted in good outcome of ADEM.

**Key Words:** acute disseminated encephalomyelitis, Japanese encephalitis, demyelination disease.

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## INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is

an acute monophasic demyelination disorder in central nervous system (CNS), typically occurs after infection or immunization<sup>(1,2)</sup>. Traditionally, ADEM is regarded

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**Table 1.** Results of cerebrospinal fluid (CSF) studies on each occasions.

	2010/08/01	2010/08/17	2010/10/14
WBC count (/μL)	46	14	6
Neutrophil (%)	23	3	0
Lymphocyte (%)	55	83	80
Gram Stain	Not found	Not found	Not found
India Stain	Not found	Not found	Not found
Glucose (mg/dL)	73	107	64
Total protein (mg/dL)	81.1	72.9	61.7
Oligoclonal band	Negative	Negative	Negative

**Table 2.** Serum titers of Japanese encephalitis virus on each occasions.

	2010/08/01	2010/08/17	2010/10/18
Serum anti-JEV IgM	Positive (0.593)*	Positive (1.11)*	Positive (0.753)*
Serum anti-JEV IgG	Negative (0.066)*	Negative (0.243)*	Positive (0.408)*

\* Optical density (OD) of patient serum reaction with viral antigen / OD of negative control serum reaction with viral antigen.

as a pediatric disease, but it is not uncommon in adult population<sup>(3-5)</sup>. Tentative diagnosis of ADEM depends on the close temporal relationship between an infection or a vaccination and clinical presentations (including fever, impaired consciousness, poly-symptomatic neurological deficits and even seizure) with diffuse white matter lesions on brain image<sup>(1,2)</sup>. Predisposing infection can be identified in about 50 to 77% of all cases, with the latency of several weeks<sup>(1,2)</sup>. Commonly reported antecedent infections include measles virus, mumps, parainfluenza virus, and herpes simplex virus<sup>(1)</sup>.

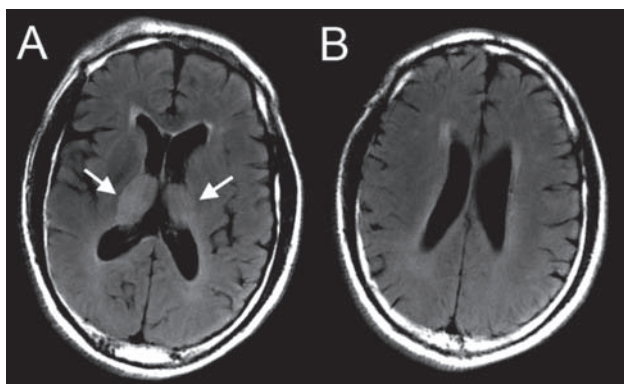
Japanese encephalitis virus (JEV) is a single stranded positive sense ribonucleic acid (RNA) virus which belongs to the family of flavivirus. It is transmitted between animals and human host by culex mosquitoes and is prevalent in Asia and Pacific Rim<sup>(6)</sup>. Most Japanese encephalitis in humans is asymptomatic. In symptomatic cases, neurological deficits include encephalopathy, febrile illness, headache and gastrointestinal symptoms<sup>(6)</sup>. Thalamic involvement on MRI is highly suggestive of Japanese encephalitis<sup>(7)</sup>. Development of ADEM after flavivirus group infection is very rare, and has only been reported previously associated with St. Louis encephalitis<sup>(9)</sup>. Post-infectious autoimmune events associated with Japanese encephalitis have been limited to case reports of JEV vaccine-related ADEM<sup>(8)</sup>. We herein

report a possible case of delayed ADEM 1-2 months after Japanese encephalitis.

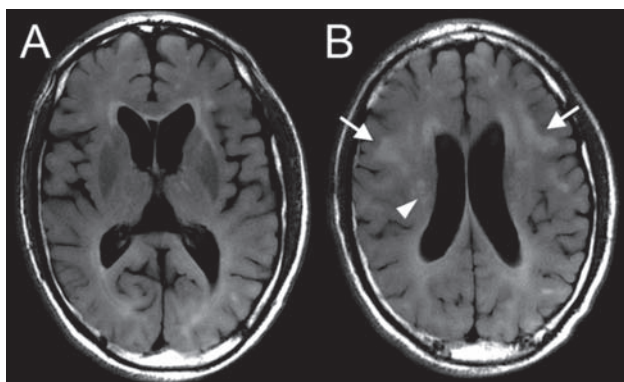
## CARE REPORT

A 50-year-old man developed headache and fever on July 28, 2010. He became irritable and inadequately responsive to questions on July 30 and was sent to the emergency room. There was neither history of toxic substance exposure nor drug abuse. He lived in the downtown area and did not travel to other place in the past few months. On examination, his Glasgow Coma Scale (GCS) was 10 (E3V2M5). His body temperature was 38°C and the neck was supple. Neurological examination did not show focal neurological dysfunction or extrapyramidal signs. An emergent cranial CT showed unremarkable finding of the brain. White blood cell (WBC) level in the peripheral blood was in the normal range and the serum CRP level was elevated to 6.53 mg/dL (normal < 0.33 mg/dL). Other laboratory examination including electrolytes, renal and liver functions were all within normal range. The cerebrospinal fluid (CSF) study on August 1st showed pleocytosis (46/μL) with elevated protein (81.1 mg/dL) (Table 1). He received intravenous acyclovir treatment under the impression of viral encephalitis after admission.

On August 2, his GCS decreased to 8 (E2V2M4). A



**Figure 1.** Axial fluid attenuation inversion recovery MRI during acute stage of Japanese encephalitis on Aug 2, 2010 shows hyperintensity lesions at bilateral thalamus (arrows) (A) without subcortical hyperintense lesion (B).



**Figure 2.** Axial fluid attenuation inversion recovery MRI during acute stage of acute disseminated encephalomyelitis on Oct 18, 2010 shows disappearance of previous thalamic hyperintense lesions (A) but new diffuse white matter lesions on bilateral juxtacortical (arrows) and periventricular (arrowhead) regions (B).

brain MRI disclosed hyperintense change of thalamus bilaterally on fluid attenuation inversion recovery (FLAIR) sequence (Fig. 1) and T2-weighted images. MR venography displayed normal cerebral venous system. Further virological study revealed positive serum anti-JEV IgM (Table 2). Other autoimmune and malignancy studies showed normal results. Acyclovir was discontinued after

the diagnosis of acute Japanese encephalitis. Under careful conservative treatment, his consciousness improved gradually. He was transferred to rehabilitation department on September 3 and was discharged on September 17. He had oriented consciousness and could walk independently without significant sequela except for mild irritable mood when discharge.

However, he suffered from a progressive confusion and delusion with violent behavior since October 8 (73 days after initial symptoms of Japanese encephalitis, 38 days after transferring to rehabilitation department, and 21 days after previous discharge, respectively) and was admitted again on October 15. His wife described that he had mistaken water for oil and refused to drink it. He was febrile to 38°C on admission. Another CSF analysis showed minimal pleocytosis (14/μL) with slightly elevated protein (72.9 mg/dL) (Table 1). Viral serological test found decrement of anti-JEV IgM antibody titer and increment of IgG titer which suggested a recovery stage from previous Japanese encephalitis (Table 2). A brain MRI on October 18 showed disappearance of previous thalamic hyperintense lesions but new multifocal hyperintense lesions of white matter on FLAIR and T2-weighted images (Fig. 2). Acute disseminated encephalomyelitis was suspected and high-dose methylprednisolone (1g/day for 5 days) was initiated. His consciousness improved gradually after high-dose intravenous steroid treatment followed by oral methylprednisolone. A repeated MRI on November 23 showed shrunken multifocal hyperintense lesions compared to previous film. He was discharged on November 27 with trivial delusion and apathetic mood. His general condition improved gradually thereafter and he went back to work six months later. A follow MRI on June 24, 2011 did not show any new T2 hyperintensity lesion.

## DISCUSSION

Our patient recovered from a virological and MRI confirmed Japanese encephalitis with typical symptoms of headache, fever and impaired consciousness. Subsequent clinical presentations of fever and psychiatric symptoms developed 1-2 months after recovery period from previous Japanese encephalitis. Diagnosis of ADEM was based on the typical clinical symptoms after a recent CNS viral

infection and newly developed multifocal hyperintense lesions on T2-weighted MR imaging. No generally accepted criteria are available for diagnosis of ADEM in adult patient currently<sup>(4)</sup>. Schwarz's concept was used in most studies for adult patients. This concept describes ADEM as the first episode of neurological dysfunctions with the evidence of demyelination on brain MRI after virus infection or vaccination without emphasis of the consciousness disturbance<sup>(5)</sup>. However, consciousness impairment was required to diagnose the ADEM in children<sup>(10)</sup>. In a latest proposed consensus, consciousness impairment with encephalopathy and demyelination on brain are required for the diagnosis of ADEM in adult<sup>(4)</sup>. The clinical presentations of our patient fit this diagnostic consensus. There is also no definite consensus criterion for MR diagnosis of ADEM. Previous studies showed ADEM usually presented as widespread, bilateral, asymmetric white matter lesions, large confluent demyelination lesion or even multiple small scattered lesions<sup>(2,11,12)</sup>. The brain MR of this patient showed multifocal hyperintense lesions involving subcortical white matter on FLAIR and T2-weighted imaging (Fig. 1), that is compatible to typical ADEM.

Another characteristic of this patient is the relative longer latency (1-2 months) between the predisposing Japanese encephalitis and the development of symptoms of ADEM. A maximal period of 3 months between vaccination and onset of ADEM is suggested. In contrast, there is no widely accepted rule for the latent periods between infection and onset of ADEM until now<sup>(1)</sup>. According to previous studies, the latency from the previous infection episode to onset of ADEM is mostly between several days to a month<sup>(1,2)</sup>. In the largest study of adult ADEM, the delay after infection or vaccination episode is  $23.3 \pm 26$  days<sup>(3)</sup>. In our patient, there was no known new infectious event between the first admission for Japanese encephalitis and the second admission for ADEM. In cases of vaccine-related ADEM, there is an exact date of vaccination. The course of Japanese encephalitis from onset day on July 28 to the recovery stage in middle September was relative long. We are not able to specify the most serious day of Japanese encephalitis and the onset day of ADEM owing to its insidious onset of initial symptoms. The latency between Japanese encephalitis and subsequent ADEM might be

within one or two months. Therefore, we proposed that this patient may have a delayed immune response of ADEM after previous Japanese encephalitis.

Post-infectious autoimmune events associated with Japanese encephalitis have been limited to case reports of Guillain-Barre syndrome after Japanese encephalitis and JEV vaccine-related ADEM<sup>(8,13)</sup>. To our knowledge, this is the first possible case report of Japanese encephalitis induced ADEM. The possible mechanism of Japanese encephalitis -induced ADEM has been explained in a recent animal study, in which severe inflammation with numerous demyelinating axons, elevated anti-myelin basic protein (MBP) antibody titer, and proliferation of MBP-specific T-lymphocytes were found in a mouse model of Japanese encephalitis<sup>(14)</sup>. The anti-myelin basic protein may cause severe CNS inflammation with subsequent demyelination<sup>(1)</sup>.

High dose steroid therapy is recommended to treat ADEM patient according to previous review articles and 50~70% ADEM patients had full recovery after treatment<sup>(1,2)</sup>. A previous report of post St. Louis virus (flavivirus group) encephalitis showed that the patient had total recovery after dexamethasone therapy as well<sup>(9)</sup>. In this case report, high dose intravenous methylprednisolone followed by oral steroid therapy in acute stage also resulted in a good outcome of ADEM.

In summary, we reported a possible case of ADEM 1-2 months after previous Japanese encephalitis. The clinical symptoms, daily function and brain images of ADEM improved after high dose steroid treatment. In patients of Japanese encephalitis with fluctuation or deterioration of consciousness during recovery stage, follow up brain MRI is warranted for possible other pathologic condition such as immune process. High dose steroid treatment is effective for immune related ADEM after previous Japanese encephalitis.

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## REFERENCES

1. Menge T, Hemmer B, Nessler S, Wiendl H, Neuhaus O, Hartung HP, Kieseier BC, Stuve O. Acute disseminated

- encephalomyelitis: An update. *Arch Neurol* 2005;62: 1673-1680.
2. Tenenbaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. *Neurology* 2007;68: S23-S36.
  3. de Seze J, Debouverie M, Zephir H, Lebrun C, Blanc F, Bourg V, Wiertlewski S, Pittion S, Laplaud D, Le Page E, Deschamps R, Cabre P, Pelletier J, Malikova I, Clavelou P, Jaillon V, Defer G, Labauge P, Gout O, Boulay C, Edan G, Vermersch P. Acute fulminant demyelinating disease: A descriptive study of 60 patients. *Arch Neurol* 2007;64:1426-1432.
  4. Liao MF, Huang CC, Lyu RK, Chen CM, Chang HS, Chu CC, Hsu WC, Wu YR, Kuo HC, Cheng MY, Hung PC, Chou ML, Lin KL, Hsieh MY, Ro LS. Acute disseminated encephalomyelitis that meets modified mcdonald criteria for dissemination in space is associated with a high probability of conversion to multiple sclerosis in taiwanese patients. *Eur J Neurol* 2011;18:252-259.
  5. Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis: A follow-up study of 40 adult patients. *Neurology* 2001;56:1313-1318.
  6. Misra UK, Kalita J. Overview: Japanese encephalitis. *Prog Neurobiol* 2010;91:108-120.
  7. Kalita J, Misra UK. Comparison of ct scan and mri findings in the diagnosis of japanese encephalitis. *J Neurol Sci* 2000;174:3-8.
  8. Plesner AM, Arlien-Soborg P, Herning M. Neurological complications to vaccination against japanese encephalitis. *Eur J Neurol*. 1998;5:479-485.
  9. Sejvar JJ, Bode AV, Curiel M, Marfin AA. Post-infectious encephalomyelitis associated with st. Louis encephalitis virus infection. *Neurology* 2004;63:1719-1721.
  10. Krupp LB, Banwell B, Tenenbaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology*. 2007;68:S7-S12.
  11. Tenenbaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: A long-term follow-up study of 84 pediatric patients. *Neurology* 2002;59:1224-1231.
  12. Singh S, Alexander M, Korah IP. Acute disseminated encephalomyelitis: Mr imaging features. *AJR Am J Roentgenol* 1999;173:1101-1107.
  13. Ravi V, Taly AB, Shankar SK, Shenoy PK, Desai A, Nagaraja D, Gourie-Devi M, Chandramuki A. Association of japanese encephalitis virus infection with guillain-barre syndrome in endemic areas of south india. *Acta Neurol Scand* 1994;90:67-72.
  14. Tseng YF, Wang CC, Liao SK, Chuang CK, Chen WJ. Autoimmunity-related demyelination in infection by japanese encephalitis virus. *J Biomed Sci* 2011;18:20.