

# Serial Magnetic Resonance Imaging and Single Photon Emission Computed Tomography Study of Acute Disseminated Encephalomyelitis Patient after Japanese Encephalitis Vaccination

TAKASHI OHYA, SHINICHIRO NAGAMITSU, YUSHIRO YAMASHITA  
AND TOYOJIRO MATSUISHI

*Department of Pediatrics and Child Health, Kurume University School of Medicine,  
Kurume 830-0011, Japan*

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**Summary:** We report a 5-year-old mentally retarded Japanese boy who developed acute disseminated encephalomyelitis (ADEM) two weeks after Japanese encephalitis vaccination (Beijing strain). He presented sudden status epilepticus, fever, and disturbance of consciousness. Initial neuroradiological findings revealed multifocal cortical swellings without any white matter lesions, suggesting the existence of partial encephalitis or focal status epilepticus. On the follow-up neuroradiological examinations, small white matter lesions were identified as having gradually extended in spite of clinical improvement by methylprednisolone pulse therapy. The cortical involvement became temporarily worse along with the extension and delayed appearance of white matter lesions. Single photon emission computed tomography (SPECT) showed marked hypoperfusion of cerebral blood flow (CBF) in the cortical lesions at both the acute and the recovery period. The serial neuroradiological findings indicated involvement of white matter and gray matter regions at different stages of the illness and a delay between the onset of symptoms and the appearance of ADEM-associated MR imaging of white-matter lesions.

**Key words** ADEM, JE vaccination, ADEM-associated MR imaging

## INTRODUCTION

Japanese encephalitis (JE) is one of the most common causes of epidemic viral encephalitis in the world, especially in South-East Asia. The annual incidence and mortality estimates for JE in South-East Asia are 30,000-50,000 and 10,000, respectively. However, this figure might be an underestimate, one study estimated the annual incidence at 175,000 per year [1]. The number of patients with JE in Japan was several thousand per year in the 1950's. Beginning in 1967, vaccination was actively recommended, the incidence was about a dozen per year in the 1980's and several per year after 1992 [2].

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous

system. It usually follows an infection or vaccination. It is clinically characterized by the acute or subacute onset of a multifocal neurological disturbance that typically follows a monophasic course. MRI findings typically reveal multifocal increased signal intensities on T2-weighted image in the white matter, subcortical white matter, basal ganglia, brainstem, or spinal cord [3]. Fourteen cases of ADEM after JE vaccination have been reported since 1991 in Japan [4]. Because some cases were severe, the Japanese Ministry of Health, Labor and Welfare recommended a suspension of JE vaccination in May, 2005.

Here we report a patient having ADEM associated with JE vaccination who showed atypical neuroradiological findings in the various stages of the illness.

Corresponding author: Toyojiro Matsuishi M.D., Ph.D, Department of Pediatrics and Child Health, Kurume University School of Medicine, 67 Asahimachi, Kurume 830-0011, Japan. Tel: 81-942-31-7565 Fax: 81-942-38-1792 E-mail: tmatsu@med.kurume-u.ac.jp

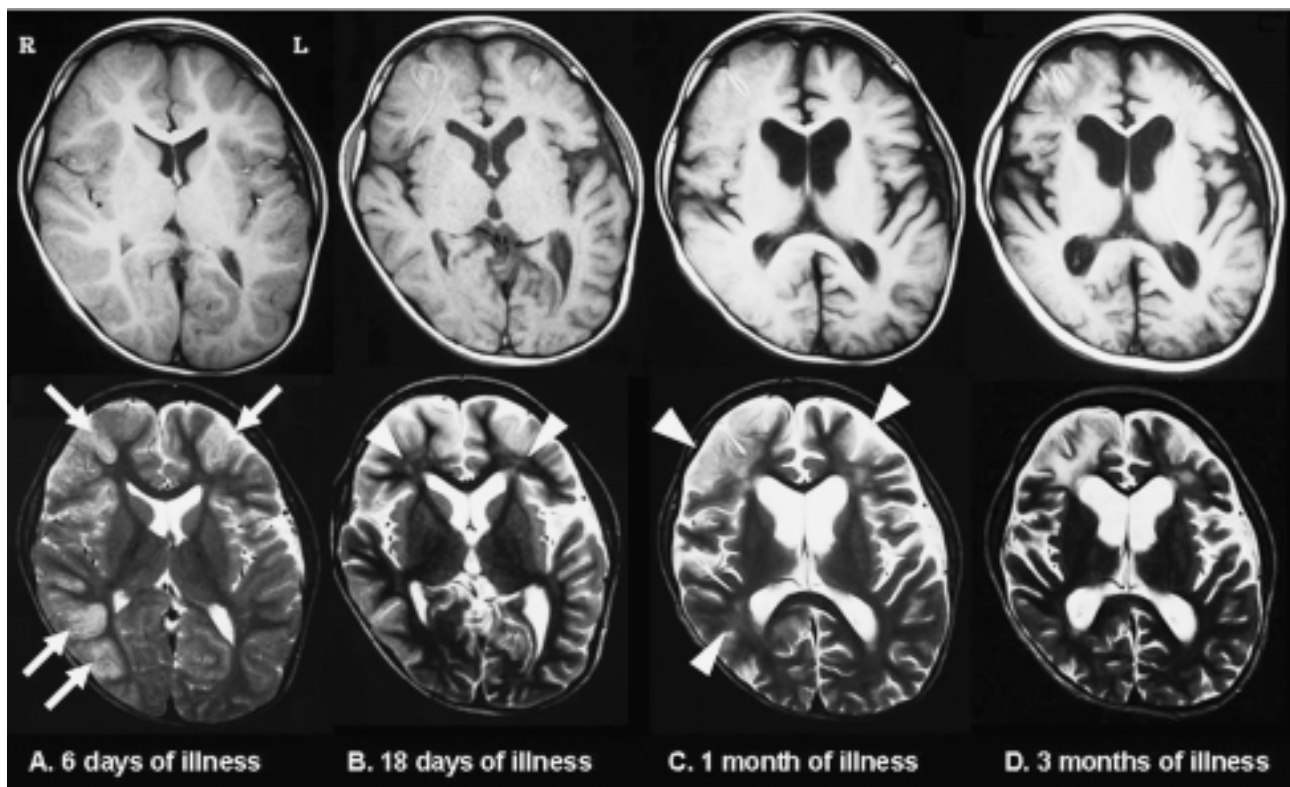
Abbreviations: ADEM, acute disseminated encephalomyelitis; CBF, cerebral blood flow; CSF, cerebrospinal fluid; JE, Japanese encephalitis; SPECT, single photon emission computed tomography.

### CASE REPORT

A 5-year-old mentally retarded boy suddenly developed generalized tonic-clonic seizure that lasted about 60 min, 2 weeks after his third JE vaccination was administered. He had been diagnosed as having delayed motor milestones, mental retardation (developmental quotient: 27), congenital anomalies of the trachea (tracheobronchial malacia, stenosis of the left main trachea), and asthma. Screening for inborn errors of metabolism was negative. Chromosome study revealed normal male karyotype. He was allergic to soybeans, wheat and corn before the onset of this episode. There was no family history of epileptic, neuromuscular, metabolic, collagen-related, vascular or demyelinating disorders. He had previously received vaccinations for measles, BCG, rubella, polio, chickenpox and mumps without any complications.

When he was admitted to Kurume University Hospital with status epilepticus, he had fever, dyspnea

with wheeze, and disturbance of consciousness. No meningeal signs were observed. The peripheral white blood cell count was increased ( $32400 /\text{mm}^3$ ) and C-reactive protein was positive (6.76 mg/dl). Serum levels of electrolytes, glucose, transaminase and ammonium were normal. Cerebrospinal fluid (CSF) contained leukocytes at  $3 /\text{mm}^3$ , all leukocytes were mononuclear cells. Total protein and myelin basic protein (MBP) in the CSF were 20 mg/dl and 377 pg/ml (normal  $<102$  pg/ml), respectively. No IgG oligoclonal band was detected. We examined JE virus hemagglutination inhibited titers and IgM (enzyme-immunoassay) of varicella-zoster virus, herpes simplex virus, cytomegalovirus and Mycoplasma pneumoniae (Particle agglutination) in CSF. They were all negative. Brain CT on admission revealed no hemorrhage or cortical edema. Electroencephalogram at 3 days of illness revealed diffuse high-amplitude delta waves without any focal epileptic discharge. At 6 days of illness, neuroradiological examinations including brain



*Fig. 1.* Magnetic resonance imaging of the brain. Upper row: T1-weighted MR imaging. Lower row: T2-weighted MR imaging. A. 6 days of illness. Cortical swellings with increased signal intensities in T2-weighted axial imaging appear in the bilateral frontal and right occipital regions (arrows). B. 18 days of illness. The cortical swelling is diminished in the bilateral frontal and right occipital regions. Increased signal intensities in the bilateral frontal white matter appear in the T2-weighted imaging (arrowheads). C. 1 month of illness. The cortical swelling and white matter lesions of bilateral frontal lobes and right occipital lobe have worsened again. (arrowheads). Marked cerebral atrophy is also seen. D. 3 months of illness. The cortical lesions have disappeared and the white matter lesions remained behind. R: right, L: left.

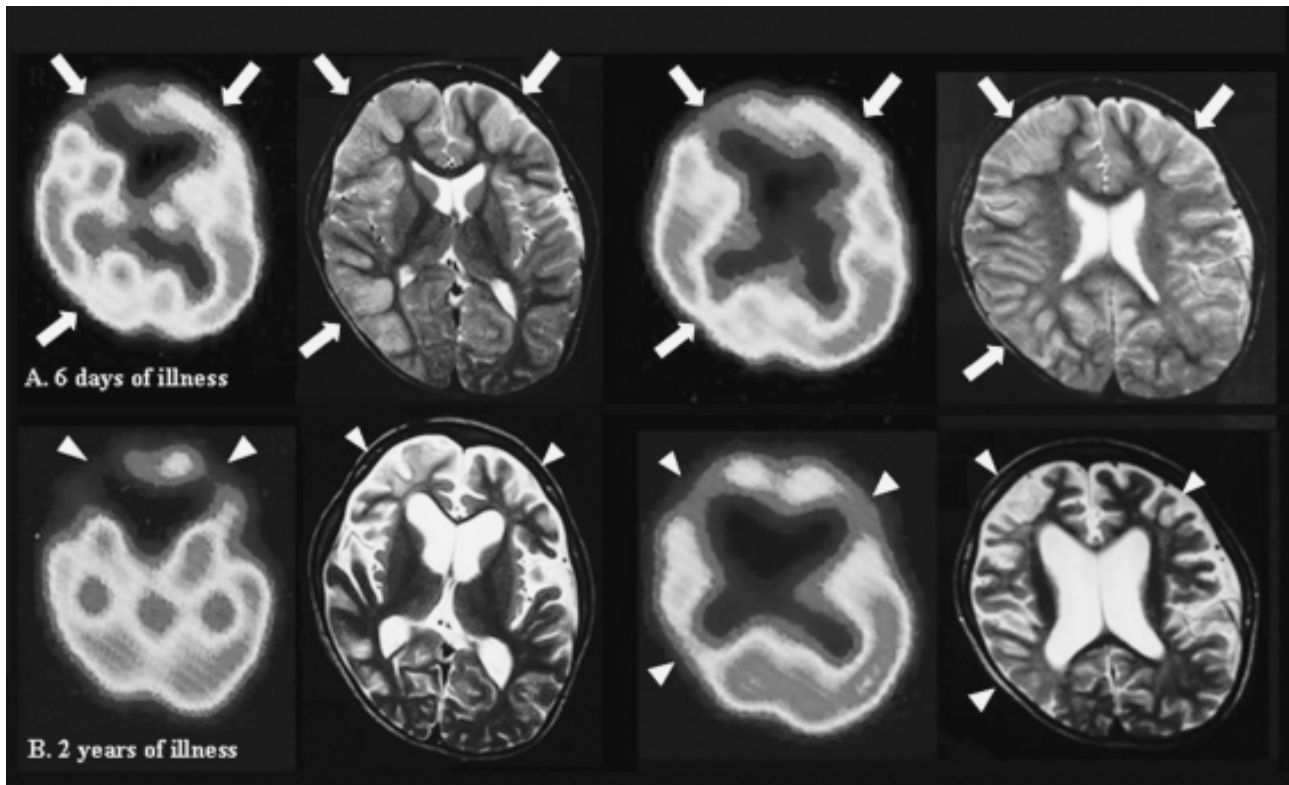


Fig. 2.  $^{123}\text{I}$ -IMP single photon emission computed tomography and T2-weighted MR imaging. Upper row: At 6 days of illness;  $^{123}\text{I}$ -IMP SPECT showed decreased cerebral blood flow (CBF) in the bilateral frontal, right occipital, and right parietal regions, where these regions had cortical swellings on MRI (arrows). In frontal regions, CBF was much decreased in the right. Lower row: At 2 years of illness; MRI showed the cortical and white matter lesions in the bilateral frontal and right parietal regions where  $^{123}\text{I}$ -IMP SPECT showed decreased CBF (arrowheads).

CT, MRI,  $^{123}\text{I}$ -IMP single photon emission computed tomography (SPECT) were performed. Brain CT revealed poor differentiation between the cortex and the white matter, and MRI showed focal cortical swellings in the bilateral frontal and right occipital regions (Fig. 1A).  $^{123}\text{I}$ -IMP SPECT showed decreased cerebral blood flow (CBF) in the bilateral frontal, right occipital, and right parietal regions, where these regions had cortical swellings on MRI (Fig. 2A). In frontal regions, CBF was much decreased in the right. Although we examined MRI of the spinal cord, it was normal at acute phase.

Initially, we suspected partial encephalitis or focal status epilepticus based on clinical symptoms and neuroradiological findings, thus, we treated the patient with intravenous administration of an antiepileptic agent and mannitol to lower intracranial pressure. However, we could not deny the existence of ADEM on account of the recent vaccination, therefore, we started methylprednisolone pulse therapy (dose; 30 mg/kg/day, 3 days a week, total 9 times) at 7 days of illness. On the follow-up MRI at 18 days of illness, increased signal intensities in the bilateral frontal

white matter were identified on the T2-weighted image (Fig. 1B), the size of these lesions showed gradual increase at 1 and 3 months of illness (Fig. 1C, D). In addition, the signal intensity in the right occipital region was increased at 1 month of illness (Fig. 1C). The focal cortical swellings in the bilateral frontal and right occipital regions were decreased at 18 days of illness, however, these regions seemed to swell again along with enlargement or delayed appearance of white matter lesions at 1 month of illness before disappearing at 3 months of illness (Fig. 1A-D). At 3 months of illness, the white matter lesions remained behind (Fig. 1D). The patient's consciousness was gradually improved at 3 days after the beginning of the methylprednisolone pulse therapy. He could smile at 9 days, maintain a sitting position at 14 days, and stand up at 24 days after the therapy. After methylprednisolone pulse therapy, prednisolone (1 mg/kg/day) was orally administered, the medication was tapered and discontinued within six months. He has shown no neurological sequel except intractable complex partial seizures with multifocal spikes.

On the follow-up neuroradiological examination

at 2 years of illness, MRI showed marked cortical atrophy predominantly in the bilateral frontal and temporal regions (Fig. 2B). MRI also showed the cortical and white matter lesions in the bilateral frontal and right parietal regions where  $^{123}\text{I}$ -IMP SPECT showed decreased CBF (Fig. 2B).

## DISCUSSION

The incidence of severe neurological complications associated with JE vaccination has been reported to be 1-2.3 per million vaccinations [5]. We previously reported seven cases of ADEM after JE vaccination [4], in which various neurological symptoms such as seizure, disturbance of consciousness, paralysis, gait disturbance, and headache, were seen. Initially, we suspected our patient of having partial encephalitis or focal status epilepticus based on his clinical symptoms and initial neuroradiological findings. However, the serial neuroradiological findings—in particular, the late appearance of abnormal signal intensities in the white matter regions, the history of JE vaccination, good clinical response to methylprednisolone therapy, and good clinical prognosis—confirmed the existence of ADEM in this patient. We also could determine that the patient did not have cerebral infarction or a progressive white matter disease such as metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe disease and other metabolic demyelinating diseases.

According to the previous literature, MRI findings of ADEM after JE vaccination typically reveal multifocal lesions predominantly in the deep white matter, thalamus, cerebellum and optic nerve, generally identified at the early stage of neurological symptoms [4]. In our case, we could detect a few characteristic MRI findings in the serial examinations. First, multifocal cortical swellings without the white matter lesions were found at the onset of neurological symptoms. Second was the late appearance of white matter lesions in spite of the improvement of clinical symptoms. Third, the cortical swellings became worse temporarily along with the enlargement or appearance of white matter lesions.

It is known that MRI findings of patients with generalized tonic-clonic seizure or status epilepticus reveal transient changes including focally increased T2 signal intensity, swelling, and increased volume of the involved cortical gyrus due to seizure-induced transient cytotoxic and vasogenic cerebral edema [6,7]. In our case, the initial cortical swellings and their diminutions between 6 days and 18 days of illness may reflect transient cortical edema due to prolonged sei-

zure activity. On the other hand, white matter lesions on MRI obtained from some patients with ADEM have been reported to appear shortly after symptom onset [8,9]. Honkaniemi et al. [8] reported three cases of ADEM in which white matter lesions did not appear until several weeks after the onset of the disease and increased during the recovery period. Kimura et al. [9] also reported that initial MR imaging failed to show ADEM-related lesions in children with postinfectious encephalitis. Although ADEM is typically described as affecting the white matter, gray matter involvement is not unusual because it also contains myelin [3,10]. Taken together, the delayed appearance of white matter lesions during a phase in which clinical symptoms was absent may indicate ADEM-related demyelination. The pathological mechanism of the delay between the neuroradiological findings and neurological symptoms remains unknown. It is important to know that both white matter and gray matter are involved at different stages of the illness and that consecutive neuroradiological evaluation is necessary if the clinical picture is suggestive for ADEM.

Because of the delay between the onset of symptoms and the appearance of ADEM-associated MR imaging, SPECT has contributed to identification of regions with functional deficits at different stages of the disease [11-13]. Okamoto et al. [12] reported that persistent hypoperfusion both at rest and in response to acetazolamide administration remained even after disappearance of hyperintensive lesions from MRI, suggesting persistent impairment of cerebral circulation affecting cognitive abilities. A previous HMPAO-SPECT study of a patient with ADEM revealed a combined pattern of hyper and hypoperfusion regions and the presence of inflammatory cells and cortical deactivation secondary to disconnection from the subcortical structures, respectively [13]. Serial SPECT study in our case showed persistent hypoperfusion in several cortical regions indicating impairment of cortical activity, which resulted from the decreased volume of the involved cortical gyrus. We cannot always detect these abnormalities on MRI. We considered that it is useful to follow serial SPECT.

In conclusion, serial MRI and SPECT may contribute to assessing the involvement of lesions and functional impairment at different stages of the disease.

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