

Fulminant Course of Acute Necrotizing Encephalopathy Followed by Serial MRI: A Case Report

급격하게 진행한 급성 괴사성 뇌병증 환자의 연속 자기공명영상 소견: 증례 보고

Ji Young Lee, MD¹, Kyung Mi Lee, MD¹, Eung Koo Yeon, MD¹, Eun Hye Lee, MD², Eui Jong Kim, MD^{1*}

Departments of ¹Radiology and ²Pediatrics, Kyung Hee University Hospital, College of Medicine, Kyung Hee University, Seoul, Korea

Acute necrotizing encephalopathy (ANE) is a rare but distinctive type of influenza-associated encephalopathy characterized by symmetric multiple lesions with an invariable thalamic involvement. Although the exact pathogenesis of ANE remains unclear, the most prevalent hypothesis is the "cytokine storm," which results in blood-brain-barrier breakdown. We present the case of a 10-year-old boy with fulminant ANE confirmed with serial MRI studies, including diffusion-weighted imaging and susceptibility-weighted imaging. A comparison of these serial images demonstrated detailed and longitudinal changes in MRI findings during the clinical course corresponding to pathophysiological changes. Our case clarifies the pathogenesis of ANE brain lesions using serial imaging studies and suggests that early immunomodulatory therapy reduces brain damage.

Index terms Infectious Encephalitis; Viral Encephalitis; Magnetic Resonance Imaging;
Neuroimaging

INTRODUCTION

Acute necrotizing encephalopathy (ANE) is a rare but devastating influenza-associated encephalopathy most prevalent in East Asia, but also described worldwide. Clinically, the disease is highly fulminant, with a rapid loss of consciousness, hepatic dysfunction, and high mortality rate; many survivors affected by severe neurologic sequelae (1, 2).

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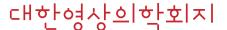
*Corresponding author
Eui-Jong Kim, MD
Department of Radiology,
Kyung Hee University Hospital,
College of Medicine,
Kyung Hee University,
23 Kyungheedae-ro,
Dongdaemun-gu, Seoul 02447,

Tel 82-2-958-8611 Fax 82-2-960-0787 E-mail euijkim@hanmail.net

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ORCID iDs

Ji Young Lee https://
orcid.org/0000-0002-1905-9446
Kyung Mi Lee https://
orcid.org/0000-0003-3424-0208
Eung Koo Yeon https://
orcid.org/0000-0001-7965-0118
Eun Hye Lee https://
orcid.org/0000-0002-8903-8528
Eui Jong Kim https://
orcid.org/0000-0003-2183-8657



Early diagnosis followed by prompt use of steroid pulse therapy along with intravenous immunoglobulin (IVIG) and antiviral agents is critical for successful outcomes (3). Given the nonspecific nature of the laboratory data usually encountered in this disease, recognition of the characteristic neuroimaging is paramount for instituting appropriate clinical measures. However, ANE is underdiagnosed due to insufficient awareness, especially during the early phase of the disease. In the following report, we describe the serial susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), and conventional MRI findings of a 10-year-old boy with ANE. We describe the clinical significance of these findings in making an accurate diagnosis, as well as pathophysiologic correlations.

CASE REPORT

A previously healthy 10-year-old boy presented to the emergency room with sudden-onset altered mental status following a 1-day prodromal illness consisting of mild fever. On arrival, he was drowsy (Glasgow Coma Scale; GCS 13) and his body temperature was 39.8°C. There was no recent history of influenza immunization. A rapid antigen test was positive for influenza B. His initial laboratory workup was unremarkable except for minimally elevated aspartate aminotransaminase (AST) of 68 U/L and alanine aminotransaminase (ALT) of 39 U/L. Cerebrospinal fluid analysis showed elevated protein and glucose without leukocytosis. Initial brain CT was unremarkable.

Six hours after admission, his level of consciousness decreased (GCS 10), he developed generalized seizures and respiratory distress. He was transferred to the intensive care unit and respiratory support by mechanical ventilation was initiated. Initial brain MRI 10 hours after the initial CT revealed high signal intensities with significant edematous changes in bilateral thalami on T2-weighted image (T2WI) and fluid-attenuated inversion recovery (FLAIR) images favoring ANE. DWI and apparent diffusion coefficient (ADC) sequences showed focal diffusion restriction in bilateral thalami. SWI showed no cerebral hemorrhage (Fig. 1A). Based on these findings, we diagnosed ANE and treatment with high-dose methylprednisolone with IVIG was initiated.

The patient declined further, becoming semi-comatose (GCS 6) on following day. Laboratory results at this time revealed severe liver dysfunction (AST, 4903 U/L; ALT, 2892 U/L) and disseminated intravascular coagulopathy (DIC), including thrombocytopenia (78000/ μ L), increased international normalized rate (2.10), elevated D-dimer level (3.85 μ g/mL), and increased fibrin degradation products (15.08 μ g/dL). A polymerase chain reaction for influenza was positive for influenza B. All other screening tests for infectious agents were negative. Based on these findings, we concluded the boy had ANE secondary to an influenza B viral agent.

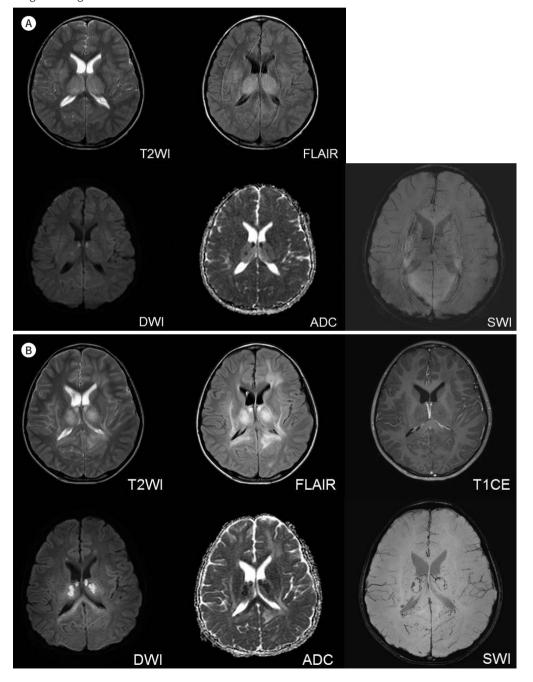
A follow-up MRI performed on the 10th day of illness revealed improvement of swelling and symmetrical high signal intensities in bilateral thalami on T2WI and FLAIR images. Distinct concentric structures on the bilateral thalami were visible on DWI and ADC sequences. The center of the lesions had lower ADC values and higher DWI values than the normal parenchyma, consistent with cytotoxic edema, and higher ADC values were detected on the periphery of the central lesions and cerebral white matter, consistent with vasogenic edema.

Fig. 1. Serial MR findings of acute necrotizing encephalopathy in a 10-year-old boy.

A. Initial MRI was done 10 hours after the first CT scan, which was unremarkable. T2WI and FLAIR images show significant edematous changes in both thalami. DWI and ADC map show focal diffusion restriction in the bilateral thalami. SWI shows no cerebral hemorrhage in the thalami.

B. Follow-up MRI was done on the 10th day of the illness. T2WI and FLAIR images show an improvement in the thalami swelling and symmetrical high signal intensities in the bilateral thalami. DWI and ADC maps show distinct concentric structures in the bilateral thalami. Restricted diffusion was also observed in the splenium of the corpus callosum. SWI shows multiple diffuse petechial intracerebral hemorrhages in the periphery of the bilateral thalamic lesions, which correlated with areas of vasogenic edema; however, central diffusion-restricted lesions in the bilateral thalami were spared.

ADC = apparent diffusion coefficient, DWI = diffusion-weighted image, FLAIR = fluid-attenuated inversion recovery, SWI = susceptibility-weighted image, T1CE = T1-weighted contrast-enhanced image, T2WI = T2-weighted image



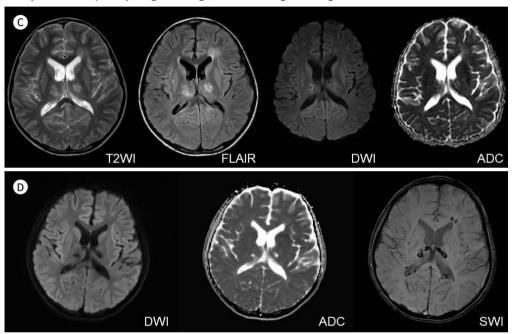
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Fig. 1. Serial MR findings of acute necrotizing encephalopathy in a 10-year-old boy.

C. Follow-up MRI was performed on the 17th day of the illness. T2WI and FLAIR images show decreased extent of signal change and swelling in the bilateral thalami with mildly aggravated hydrocephalus. DWI and ADC maps show almost complete resolution of the diffusion abnormalities in the bilateral thalami and splenium of the corpus callosum.

D. Follow-up MRI was performed six months after the illness. On DWI and ADC maps, identifiable diffusion-restricted lesions were no longer visible. SWI shows a decreased extent of multifocal microhemorrhages and remained hemosiderin deposition in the bilateral thalami.

ADC = apparent diffusion coefficient, DWI = diffusion-weighted image, FLAIR = fluid-attenuated inversion recovery, SWI = susceptibility-weighted image, T2WI = T2-weighted image



Restricted diffusion was also seen in the splenium of the corpus callosum. SWI demonstrated petechial intracerebral hemorrhages in the periphery of bilateral thalamic lesions and cerebral white matter, however central diffusion restricted lesions in bilateral thalami were spared. Gadolinium-enhanced T1WI revealed no marked enhancement (Fig. 1B).

A follow-up MRI on the 17th day of illness after another course of methylprednisolone pulse therapy revealed remarkable improvement of bilateral thalamic lesions. Diffusion abnormalities in bilateral thalami and splenium of the corpus callosum had resolved or nearly resolved (Fig. 1C).

After being comatose for four weeks, the patient regained consciousness and continued to improve, eventually regaining speech and gross motor function in all extremities. A follow-up MRI on six months after his illness revealed decreased extent of multifocal microhemorrhages and remained hemosiderin deposition with encephalomalacic changes in bilateral thalami, and identifiable diffusion restricted lesions were no longer visible (Fig. 1D).

All procedures have been conducted according to the principles embodied in the Declaration of Helsinki 1964 and its later amendments.

DISCUSSION

The etiology and pathogenesis of ANE remains unclear. About 90% of patients with ANE have a history of viral infection, making the most widely accepted hypothesis hypercytokinemia (4) associated with viral infection. Overproduced cytokines ("cytokine storm") cause vascular endothelial damage and increase the permeability of the vessel walls in multiple organs, including the brain. This results in systemic response such as systemic inflammatory response syndrome like shock, multiple organ failure and DIC as observed in our patient. In line with this hypothesis, neuropathologic examinations revealed edema, petechial hemorrhage and necrosis in ANE lesions (2, 5).

On neuroimaging examination, symmetrical, multifocal lesions are the most distinctive feature of ANE. The thalamus is the most frequently affected structure, followed by the upper brain stem tegmentum, the cerebral white matter, and the cerebellar medulla (5). Another typical feature of ANE is a concentric tricolor pattern structure, which is seen most obviously on ADC images, consisting of the inner and outmost layers of facilitated diffusion and middle layer of restricted diffusion (5). This correlates with reported pathological changes. The center of the lesions shows perivascular hemorrhage, and necrosis of neurons and glial cells corresponds to slightly high signals on ADC, while the periphery of the center portion revealed congestion of arteries, veins, and capillaries and acute swelling of oligodendrocytes corresponding to low signals in the surrounding tissue, with extravasation at the edge of the lesions corresponding to high signals in the outermost areas (5).

In our case, we could observe interval changes on serial MRIs. On the day of admission, development of high signal intensities in the swollen bilateral thalami was seen on T2WI compared to the initial CT taken several hours prior. There was a limited diffusion restriction and no evidence of hemorrhage on DWI/ADC and SWI sequences. The following day, his mental status deteriorated to a semicoma, and he had a drastically elevated serum aminotransferase with DIC, suggesting an acute and fulminant inflammatory response. Repeated MRI scan on the tenth day revealed gradual resolution of edema and interval development of cytotoxic edema (larger diffusion restricted lesions) as well as petechial hemorrhage within the area of diffuse vasogenic edema in the bilateral thalami. Bicolor concentric structures of central low signal (cytotoxic edema) surrounded by lesions of high signal (vasogenic edema) were seen on ADC sequences, which was somewhat different from the typical tricolor pattern. Central high signals, which might represent a lesion of hemorrhagic necrosis, were not obvious. In our case, early intensive treatment might have minimized brain injury, and prevented tissue necrosis. A repeated MRI scan on the seventeenth day of illness and six months after the onset of illness showed gradual recovery diffusion restricted lesions and sequelae of ANE including residual hemosiderin and encephalomalacic changes.

Restricted diffusion was also observed in the splenium of the corpus callosum, which is not a typical radiologic appearance of ANE. In this case, splenial lesions of the corpus callosum were located centrally and symmetrically, and recovered completely within a week, unlike other disease affecting corpus callosum, such as acute disseminated encephalomyelitis. Similar MR findings have been reported in some cases of infectious encephalopathy with different causative agents, including influenza, and the pathogenesis of reported cases was

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postulated to be intramyelinic edema and inflammatory infiltrate (6). Transiently decreased ADC values in the present patients suggest that quickly resolved intramyelinic edema and inflammatory infiltrate may be the operant factor.

In addition, our case revealed petechial hemorrhages in the periphery of the thalamic lesions and in the cerebral white matter, which correlated with areas of vasogenic edema. Previous studies have demonstrated hemorrhage occurs predominantly in the central portion of the involved deep gray matter but not in the cerebral white matter (7-9). Multifocal cortical and subcortical microhemorrhages including white matter are frequently seen in patients with thrombotic microangiopathy caused by disorders such as DIC (10). Vascular endothelial damage and increased permeability secondary to the viral infection might be involved in the development of hemorrhage in this case. The location of hemorrhage (within the area of vasogenic edema) and the timing of hemorrhage (after development of DIC) support this.

Our case clarifies the pathogenesis of an ANE brain lesion with serial imaging study and suggests that early immunomodulatory therapy reduces brain damage. Early recognition and diagnosis of ANE based on detailed neuroradiological imaging methods including DWI/ADC and SWI will facilitate potential life-saving treatment and supportive therapies.

Author Contributions

Conceptualization, L.J.Y., L.K.M., K.E.J.; data curation, L.J.Y., L.K.M., K.E.J., L.E.H.; investigation, L.J.Y., Y.E.K.; methodology, L.J.Y., Y.E.K.; resources, K.E.J., L.E.H.; supervision, K.E.J.; visualization, L.J.Y.; writing—original draft, L.J.Y.; and writing—review & editing, L.J.Y.

Conflicts of Interest

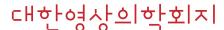
The authors have no potential conflicts of interest to disclose.

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급격하게 진행한 급성 괴사성 뇌병증 환자의 연속 자기공명영상 소견: 증례 보고

이지영1 · 이경미1 · 연응구1 · 이은혜2 · 김의종1*

급성 괴사성 뇌병증은 드물지만 특징적인 인플루엔자 관련 뇌병증으로, 시상을 포함한 영역의 좌우 대칭의 다발성 병변을 특징으로 한다. 급성 괴사성 뇌병증의 정확한 발병 기전은 아직까지 불분명하나, 사이토카인 과분비에 의한 혈액뇌장벽의 파괴가 가장 널리 받아들여지는 가설이다. 저자들은 급격하게 진행한 10세 남아의 급성 괴사성 뇌병증 증례를 확산강조영상과 자화강조영상을 포함한 연속 자기공명영상 소견과 함께 보고하고자 한다. 연속 자기공명영상에서 나타나는 뇌병변의 시간적 변화는 임상경과 및 병태생리학적 변화와 일치되는소견을 보였다. 본 증례는 연속 자기공명영상 소견을 통해 급성 괴사성 뇌병증 뇌병변의 발생 기전을 명확히 하였으며, 더 나아가 빠른 면역조절치료를 통해 뇌 손상의 정도를 줄일 수 있음을 시사하였다.

경희대학교 의과대학 경희대학교병원 ¹영상의학과, ²소아청소년과