이상성 경련과 후기 확산 감소를 동반하는 급성 뇌병증: 증례보고와 분석연구

영남대학교 의과대학 소아청소년과¹, 영상의학과²

박선영¹ · 이재민¹ · 홍재범² · 김세윤¹

Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion (AESD): Case Report and Review of the Literature

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a recently established subtype of encephalopathy syndrome. AESD is characterized by febrile status epilepticus on the first day, followed by transient recovery of consciousness. A secondary cluster of complex seizures follows on day three to six, and reduced diffusion in the subcortical white matter can be observed by magnetic resonance imaging (MRI). Affected children have neurological sequelae of varying severity. The exact pathogenesis of AESD is unclear and clinicians often empirically manage patients with steroid pulse therapy and intravenous immunoglobulin. We herein report a case of a 13-month-old girl who was transferred to our hospital because of a secondary episode of afebrile seizures five days after a brief febrile convulsion. On day seven, diffusion-weighted MRI and the calculated apparent diffusion coefficient map indicated restricted diffusion in the subcortical white matter of both frontal lobes, the posterior cingulate gyrus, and the genu of the corpus callosum. Because the patient had no neurologic abnormalities after the second cluster of seizures, she underwent close observation with no medical treatment. She recovered completely without neurological sequelae and follow-up MRI on day 36 showed resolution of the restricted diffusion.

Key Words: Encephalopathy, Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), Seizure, Influenza, Diffusion weighted image

Sun Young Park, MD¹, Jae Min Lee, MD, PhD¹, Jae Beom Hong, MD², Saeyoon Kim, MD, PhD¹

Departments of Pediatrics¹, Radiology², College of Medicine, Yeungnam University, Daegu, Korea

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Correspondence to Saeyoon Kim, MD, PhD
Department of Pediatrics, Yeungnam University Medical Center, 170 Hyungchungno, Nam-gu, Daegu 42415, Korea

Tel: +82-53-620-3533, Fax: +82-53-629-2292

E-mail: sysnow88@hanmail.net

Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a unique subtype of acute encephalopathy in children. The initial neurological symptom is a febrile seizure usually lasting more than 30 minutes (early seizure); this is followed by late seizures, most often a cluster of complex partial seizures, and subsequent deterioration of consciousness. The initial magnetic resonance imaging (MRI) findings are typically normal, but a subcortical white matter lesion, later develops. This lesion is most obvious on diffusion weighted imaging (DWI). However, the lesion eventually disappears, and affected patients have varying degrees of neurologic sequelae^{1,2)}.

The exact pathogenesis of AESD is unclear. It has been suggested to be related to excitotoxic injury with delayed neuronal death²⁾. AESD is a common subtype of acute encephalopathy in children. Methylprednisolone pulse therapy and intravenous immunoglobulin have been recommended for patients with influenza encephalopathy regardless of the clinico-radiological findings, and this treatment is also given for most cases of AESD³⁾.

Since the first AESD cases were reported in 2006 in Japan, AESD have been approved to be the most common subtype of acute para-infectious encephalopathy in Japan⁴⁾. However, there has been only one reported case of mild influenza-associated AESD in Korea⁵⁾. We herein report a case of a 13-month-old girl with a mild form of AESD associated with influenza B infection. She completely recovered after conservative treatment without steroid pulse therapy or intravenous immunoglobulin.

Case report

A 13-month-old girl who had been admitted to the hospital four days earlier with febrile convulsion was transferred to our hospital because of another episode of afebrile seizures. During the first episode, she had experienced a generalized tonic-clonic

convulsion lasting one to two minutes following a 24-hour prodromal illness consisting of a high fever and cough. The first episode was controlled by intrarectal administration of diazepam. She was alert after the convulsion, and her neurological examination findings were unremarkable. A rapid antigen detection assay from a nasopharyngeal swab revealed influenza B. She was diagnosed with febrile seizures associated with influenza B. Treatment with oseltamivir phosphate was begun, and her fever disappeared by day two.

On day five, she had completely recovered and was recommended for discharge, but she developed an afebrile atonic seizure lasting one to two minutes, followed by disturbance of consciousness for about four hours. She was then brought to the emergency department of our hospital. In the emergency room, she had another atonic seizure and diazepam was administered. Electroencephalography was performed to determine whether she was in status epilepticus, but it showed no abnormal activity. That night, she had a cluster of five clinical seizures, each lasting one to three minutes, and we began treatment with an anti-epileptic drug. MRI was performed on the seventh day of illness; DWI and the calculated apparent diffusion coefficient (ADC) map revealed restricted diffusion in the gray matter and subcortical white matter (dominantly subcortical white matter) of both frontal

Fig. 1. MRI on day 7. Diffusion weighted imaging (DWI) (A, D) shows high signal intensity and the apparent diffusion coefficient (ADC) map (B, E) shows low signal intensity in the subcortical white matter of both frontal lobes, the posterior cingulate gyrus and the genu of the corpus callosum. Fluid attenuated inversion recovery (FLAIR) imaging (C, F) shows gyral swelling and subtle high signal intensity around the lesions.

lobes, the posterior cingulate gyrus, and the genu of the corpus callosum; the restricted diffusion was bilaterally symmetrical (Fig. 1A, B, D, E). Fluid attenuated inversion recovery (FLAIR) images showed gyral swelling and subtle high signals around the lesions without enhancement (Fig. 1C, F). We performed a lumbar puncture to check for encephalitis, but there was no evidence of infection. On day eight, a second MRI with magnetic resonance spectroscopy was performed to rule out metabolic encephalopathy. The high signal intensity on DWI had disappeared from subcortical areas, but was prominent in the overlying cortical gray matter (Fig. 2A, D). The ADC map showed an increased ADC within the subcortical white matter (Fig. 2B, E). FLAIR images showed minimal swelling and high signal intensity in the posterior cingulate gyrus (Fig. 2C, F). Magnetic resonance spectroscopy showed no specific findings. The patient's biphasic clinical course and delayed radiological features were consistent with AESD; therefore, she diagnosed with a mild form of AESD. She recovered completely without neurological sequelae. Follow-up MRI on day 36 showed resolution of the restricted diffusion in both the white matter and cerebral cortex.

Discussion

AESD is a recently established encephalopathy syndrome diagnosed both by its clinical manifestations and imaging findings. A prolonged (>30 minute) febrile seizure is the initial neurological symptom on day one; this is followed by secondary seizures, most often a cluster of complex partial seizures, and deterioration of consciousness on days four to six. Influenza virus A and B and human herpesvirus 6 and 7 are the most common pathogens associated with AESD, but the exact pathogenesis of AESD remains unclear³.

Acute encephalopathy affects 400 to 700 children per year in Japan. AESD is the most common subtype of acute encephalopathy, accounting for about 30% of all cases⁴. AESD was established as a distinct type of acute encephalopathy in the 1990s⁶. An overwhelming number of cases of AESD occur in Japan compared with other countries, and most reports are from Japan⁷. In Korea, a case of mild influenza-associated AESD was reported in 2015⁵. A 24-month-old girl diagnosed AESD due to her biphasic clinical course and MRI finding, but unlike typical AESD, she started with a brief febrile seizure instead of febrile status epilepticus and her

Fig. 2. MRI on day 8. Subcortical high signal intensity on Diffusion weighted imaging (DWI) (A, D) has disappeared. However, high signal intensity in the overlying cortical gray matter has become prominent. The apparent diffusion coefficient (ADC) map (B, E) shows high signal intensity within the subcortical white matter, which had been low on day 7. Fluid attenuated inversion recovery (FLAIR) imaging (C, F) shows minimal swelling and high signal intensity in the posterior cingulate gyrus.

symptoms had fully recovered without any neurologic sequelae. The clinical course of our patient was mostly consistent with this previous report. She had a brief febrile seizure associated with influenza B infection on day one, followed by a secondary cluster of seizures and disturbance of consciousness on day five. MRI findings on day seven revealed reduced subcortical diffusion. Fortunately, the patient's seizure was immediately controlled by intrarectal administration of diazepam. The delayed clinical and radiological features were consistent with AESD, and she was therefore diagnosed with AESD despite the short duration of the initial seizure.

Acute neurologic manifestations are usually regarded as uncommon complications of influenza infection, and this condition is even rarer when associated with influenza B virus⁽⁸⁾. Lin et al. reported a 12% incidence of neurological manifestations associated with influenza B infection in children, ranging from mild symptoms to severe necrotizing encephalitis⁽⁸⁾. A recent retrospective study including patients with laboratory-confirmed influenza B during the 2012 winter/spring influenza epidemic reported a 7.9% (28/355) incidence of neurological or muscular complications. Febrile seizure was the most common adverse event (67.9%) and the characteristics of febrile seizure associated with influenza B infection are generally similar to those of other febrile seizures, apart from the greater age at the time of the first seizure⁽⁹⁾.

AESD is clinically characterized by biphasic seizures and the secondary seizures most often appear in a cluster of complex partial seizures^(1,3). Between the biphasic seizures, patients seem to have recovered consciousness, although they may exhibit slightly reduced responsiveness, an absent-minded appearance, or subtle disorientation⁽⁷⁾. Involuntary stereotypic movements (e.g., hand-washing movements; or choreic movements) are often observed beginning on day four to 18. After recovering from the secondary episode, focal neurological signs arising from the frontal cerebral cortex become apparent, such as reduced spontaneity and aphasia. The mortality rate is low (<5%)⁽³⁾. The patient in this report developed secondary seizures and disturbance of consciousness on day six. Even in retrospect, it was not possible to differentiate her condition from a simple brief febrile seizure based on clinical features alone. Moreover, it is not practical to perform MRI for all patients with a brief febrile seizure. Although our patient recovered completely without any neurologic sequelae, the outcomes of patients with AESD range from normal to severe mental retardation, paralysis, epilepsy, and even death (<5%). Recently, several studies attempted to identify clinical, laboratory, neuroradiological and electroencephalography findings useful for differentiating AESD from prolonged febrile seizures (PFS) in acute stage, and also to develop a scoring sys-

tem for predicting AESD^(7,10). A scoring system of Tada et al.⁽¹⁰⁾ is consist of low consciousness level 12–24 hours after seizures, age below 1.5 years, duration of convulsions above 40 minutes, mechanical ventilation, aspartate aminotransferase on admission above 40 mEq/L, blood glucose on admission above 200 mg/dL, creatinine on admission above 0.35 mg/dL and another scoring system of Yokochi et al.⁽⁷⁾ is consist of potential hydrogen (pH) <7.014, serum alanine transaminase ≥ 28 IU/L, blood glucose ≥ 228 mg/dL, time until waking ≥ 11.0 hours, serum creatinine ≥ 0.3 mg/dL, serum ammonia ≥ 125 μ g/dL. According to both scoring system, our patient cannot be predicted to have AESD and we think that it is because as those previous studies were conducted to patients with ES lasting longer than 30 minutes. Clinicians caring for children should recognize and inform the parents about the possible secondary progression around day five and remain vigilant for neurologic complication of influenza B virus infection, especially if they are in East Asian countries.

In previous studies, magnetic resonance spectroscopy in children with AESD revealed a decreased *N*-acetylaspartate concentration and an elevated glutamate/glutamine complex concentration during the week of presentation. The glutamate/glutamine complex concentration subsequently normalized; however, the *N*-acetylaspartate concentration remained low in two patients with neurologic sequelae but became nearly normal in the third patient without neurologic sequelae. These findings suggest that excitotoxic neuronal damage plays an important role in the pathogenesis of AESD and that magnetic resonance spectroscopy may help predict outcome⁽¹¹⁾. In our case, however, the magnetic resonance spectroscopy results were not consistent with these previous findings. Beside MRS finding, several prognostic factors had been analyzed, because acute encephalopathy with reduced subcortical diffusion (AED) covers a spectrum including not only typical AESD but also atypical AESD with monophasic clinical course, or more severe subtypes. Hayashi et al.⁽¹²⁾ revealed that prolonged seizure at the onset and loss of consciousness 24 hours after the onset to be poor prognostic factors. In the study of Azuma et al.⁽¹³⁾, higher creatinine and LDH levels and lower platelet counts in the acute phase correlated with poor prognosis. As our patient had a brief febrile seizure at the onset, immediately recovered alertness after convulsion and had normal values of serum creatinine, LDH, platelet counts, she could have been expected to have good prognosis.

Steroid pulse therapy, intravenous immunoglobulin, and therapeutic hypothermia have been recommended for patients with influenza encephalopathy and acute necrotizing encephalopathy, and most patients who were finally diagnosed with AESD were conventionally treated with these agents. However, there is no

evidence of their efficacy in patients with AESD²⁾. Attempts have been made to identify the predictive factors for AESD because a delayed diagnosis and therapeutic intervention for encephalopathy are associated with poorer neurologic outcomes¹²⁾. However, our patient completely recovered without these therapies. Only an anticonvulsant was used to control her seizure. Hayashi et al.¹²⁾ reported that steroids and/or immunoglobulin did not show significant treatment efficacy, and they suggested that this was due to the pathogenetic differences among the subtypes of acute encephalopathy. Recent studies have suggested a close relationship between AESD and excitotoxicity but the pathogenesis of AESD remains unclear. Thus to improve neurologic outcomes with proper treatment, it will be important to first clarify the pathogenesis.

In conclusion, AESD is a common subtype of acute encephalopathy, especially in children in East Asia. Although it is the most common subtype among children in Japan, this is the second published report of AESD in Korea, and we believe that many cases are overlooked. Therefore, clinicians must be able to identify potentially affected patients, closely observe their neurologic manifestations and diagnose AESD. Moreover, our report provides evidence that patients with AESD must be managed with proper treatment according to their individual condition. The accumulation of retrospective studies of patients with AESD may help to elucidate the pathophysiology of this disorder and establish an optimal treatment regimen.

요약

이상성 경련과 후기 확산 감소를 동반하는 급성 뇌병증(AESD)은 최근 확립된 뇌병증 증후군의 한 아군이다. AESD는 특징적으로 첫날 열성 간질 중첩증이 발생하고 이후 일시적인 의식의 회복을 보인다. 3일에서 6일경 두 번째로 복합 발작이 연속적으로 무리지어 발생하고 자기공명영상에서는 피질하 백질의 확산이 감소된다. 이환된 환아는 다양한 정도의 신경학적 후유증을 가지게 된다. AESD의 발병기전은 명확히 밝혀지지 않았으며 임상자들은 경험적으로 스테로이드 충격 요법과 정맥 글로불린으로 치료한다. 이번 발표에서 13개월된 여아는 짧은 열성경련에 이후 5일경 발생한 두 번째 비열성 경련으로 본원으로 전원되었으며 7일경 시행한 확산강조영상과 겔 보기확산계수 지도에서 양측 전두엽의 피질하 백질과 후측대상회, 뇌량의 무릎에서 확산이 제한된 소견을 보였다. 환아는 두 번째 경련 이후 신경학적 이상이 동반되지 않았기 때문에 약물치료 없이 철저히 경과관찰 하였으며 신경학적 합병증 없이 완전히 회복되었고 36일째 확인한 자기공명영상에서도 확산의 제한이 소실되었다. 이번 발표는 한국에서 처음으로 발표된 AESD 사례로, 경한 신경학적

증상을 보이는 AESD의 치료에 대한 지침을 마련하는데 도움이 될 것이다.

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