이상성 발작과 후기 확산 저하를 동반한 경한 인플루엔자 뇌병증 1례

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A Case of Mild Influenza-Associated Encephalopathy with Biphasic Seizures and Late Reduced Diffusion in Korea

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Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is one form of encephalopathy that has a biphasic clinical course and a typical magnetic resonance imaging (MRI) finding of reduced diffusion in the frontal or frontoparietal subcortical white matter, with sparing of the perirolandic region. There have been no previous reports of influenza-associated AESD in Korea, while approximately 20 cases per annum have been reported in Japan. We report a 24-month-old Korean female with a clinically, radiologically diagnosed mild form of AESD associated with influenza A. The patient had a complex partial seizure on the second day of fever, followed by a cluster of brief seizures on the fifth day of viral febrile disease. MRI showed diffusion restrictions on the subcortical white matter and cortex of both frontoparietal lobes. Influenza A was proven after her temperature had fallen. Her clinical symptoms improved gradually without using oseltamivir, and no other neurologic sequelae remained. This case report is the first reported mild form of influenza-associated AESD in Korea. The ethnicity and regionality of influenza-associated encephalopathy should be widely studied.

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

Introduction

Much research about the influenza virus has been conducted due to its outbreaks and seasonal presentation. Influenza virus infection is usually accompanied by mild and self-limiting respiratory symptoms such as fever, headache, cough, and sore throat. In addition to the typical symptoms of influenza infection, a variety of neurologic complications have been noted including encephalopathy, seizures, Reye syndrome, Guillain-Barre syndrome, and transverse myelitis¹⁾. During the past decade, influenza-associated encephalopathy has gained much attention because influenza became the most common cause of encephalopathy in Japan^{1,2)}.

Influenza-associated encephalopathy is divided into at least four types: acute

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necrotizing encephalopathy (ANE), hemorrhagic shock and encephalopathy syndrome (HSES), clinically mild encephalitis/encephalopathy with a reversible splenic lesion (MERS), and Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)³⁾.

Since the first AESD cases were reported in 2006 in Japan, approximately 20 cases of influenza-associated AESD have been reported recently^{4,5)}. Several cases of the mild form of influenza-associated AESD have also been reported in Japan³⁾. However, there are no previous reports of influenza-associated AESD in Korea. We herein report a 24-month-old Korean female who experienced a mild form of AESD associated with influenza A.

Case Report

A previously healthy 24-month-old Korean girl visited our emergency department due to a cluster of brief convulsions. She was born at full term weighing 3.7 kg through normal vaginal delivery and had a history of simple febrile convulsion when she was 17 months old.

Four episodes of right arm tonic seizures lasting approximately two minutes were repeated before her emergency department visit. A fever of 38.3°C was recorded in the emergency department without any upper respiratory infection symptoms. It was her fifth day of fever. Upon arrival at our emergency department, the patient had a generalized tonic-clonic seizure lasting 20 minutes, which stopped after two serial administrations of intravenous lorazepam and phenobarbital. Her mental status was drowsy, while pupil light reflex and extremity deep tendon reflexes seemed normal.

Initial complete blood cell counts, electrolytes, erythrocyte

sedimentation rate (ESR), and C-reactive protein (CRP) were normal, whereas aspartate transaminase was elevated (113 IU/L). Spinal tapping was performed, and routine cerebrospinal fluid (CSF) assay white blood cell (WBC) count was 1/uL, glucose level was 114 mg/dL, and protein level was 25.3 mg/dL. Magnetic resonance imaging (MRI) showed reduced diffusion in the frontal lobes and both parietal lobes (Fig. 1). We started antibiotics and antiviral agents assuming encephalitis.

Three days before admission, she had visited our emergency department after a complex partial seizure for one minute followed by 10 minutes of postictal confusion. The patient had high fever the day before the initial seizure without any upper respiratory infection symptoms. She had acute otitis media in both ears. Her mental state was alert, and other neurologic exams were all normal. Complete blood cell counts, electrolytes, ESR, and CRP were normal, and a rapid influenza diagnostic test from a nasopharyngeal swab was also negative. She was discharged after several hours of close observation for further convulsion. After discharge, the patient's consciousness had been altered, with a decreased response to verbal and physical stimulants for one day. She had slept all day long, being lethargic for about 24 hours. Subsequently, her consciousness had been recovered with normal verbal and physical responses until the day of cluster seizure.

There were no further seizures after intravenous phenobarbital administration, and she was admitted to our hospital. On the first day of admission, the patient's mental status improved so that her movement, feeding, and response to verbal stimuli became intact. However, her mood was aggressive, and she had a problem with spontaneous speech. She did not speak any words, except to say "Father" once.

On the second day after admission, her temperature fell and

Fig. 1. MRI findings. Diffusion weighted imaging (DWI) on the day of brief seizures shows high signal lesion in the frontal subcortical white matter (A). Apparent diffusion coefficient (ADC) reveals reduced diffusion in the frontal lobes (B), and both parietal lobes with sparing of perirolandic region (C).

Fig. 2. Electroencephalogram on the second day of admission, which is performed during sleep, shows intermittent, irregular delta waves on the patient's frontal lobe. Otherwise, no epileptic form discharges were observed.

her mood became stabilized. She spoke sentences composed of more than two words, and her movement became active. An electroencephalogram was performed that showed intermittent, irregular delta waves on her frontal lobe. Otherwise, no epileptiform discharges were seen (Fig. 2).

On the fifth day after admission, fever and upper respiratory infection symptoms were clearly absent, and both instances of acute otitis media improved. A respiratory virus test (PCR) from a nasopharyngeal swab revealed influenza A. Blood, urine, and CSF cultures were negative, and PCR tests for enterovirus and herpes simplex in CSF fluids were also negative. We did not add oseltamivir due to her improving states of symptoms. She was discharged on the seventh day after admission, with mild speaking fluency problems remaining as neurological sequelae. At her visit to our outpatient clinic 10 days after discharge, her mental status was alert, and her speaking fluency was also improved.

Discussion

AESD, also known as acute encephalopathy with febrile convulsive status epilepticus (AEFCSE), was first described in a Japanese journal⁵. As described previously, it has typical findings of biphasic clinical course and typical MRI findings of reduced diffusion in the frontal or frontoparietal subcortical white matter, with sparing of the perirolandic region⁵. Typical AESD usually starts with prolonged febrile seizure over 30 minutes on the first day of a viral febrile disease. On the second day, consciousness recovers slowly in most cases. On the fourth or fifth day, most cases have a cluster of brief convulsions⁶. Typical AESD has low

fatality (1%) and high probability of neurologic sequelae (66%), including reduced spontaneity, aphasia, apraxia, and hemiparesis⁷. In recent study about prognosis of AESD, most of 44 cases of AESD experienced mild to severe cognitive or gross motor impairment and 23% of patient experienced post-encephalopathic epilepsy (PEE) After the event of AESD⁸. In our case, we could diagnose AESD due to her biphasic clinical course and MRI findings, but unlike typical AESD, she started with a brief febrile seizure instead of febrile status epilepticus. Also, her symptoms had fully recovered without any neurologic sequelae. Such a mild clinical course of AESD cases has been reported in Japan as 'mild form AESD'³.

The main pathophysiologic mechanism of AESD is excitotoxicity that high levels of exotoxins, for example glutamate, could cause delayed or apoptotic neuronal death⁶. It has been demonstrated that genetic predisposition also has a significant role in AESD. Known genes that are associated with AESD are carnitine palmitoyltransferase 2 (CPT2), adenosine A2A receptor (ADORA 2A), and sodium channel subunits 1A (SCN1A) and SCN2A^{9,10}. However, the biologic, genetic studies for AESD are ongoing, and many pathophysiologies remain ambiguous. The number of case reports about influenza-associated encephalopathy have been weighted toward Japan, while a few cases have been reported in other countries such as Australia, Canada, and Turkey¹¹. There was only one case in the United states, and the patient was Japanese¹¹. As this is the first case report in Korea, it could have significance with respect to whether Asians have a higher prevalence than other European or American countries.

The most common etiologies of AESD are influenza virus and human herpes virus (HHV) 6 and 7¹². Among 17 recent cases of AESD in Japan, four cases were caused by the influenza virus, and another four cases had HHV infection⁵. Some studies have suggested the use of theophylline as a risk factor for AESD⁶. Several diagnostic methods are available for the detection of the influenza virus. Rapid influenza diagnostic tests, immunofluorescent assays, molecular assays including real-time PCR (RT-PCR), and viral cultures are available¹³. In outpatient clinics and emergency departments, rapid influenza diagnostic tests are commonly used because they are simple to perform and produce quick results (approximately 10 to 15 minutes). In spite of its convenience, the sensitivity of the rapid influenza diagnostic test is quite low, being 62.3%, with high specificity (98.2%)¹³. Compared with the rapid influenza diagnostic test, RT-PCR or viral culture has higher sensitivity (64.6%) and specificity for the detection of the influenza virus¹³. In our case, the rapid influenza diagnostic test was normal at the first event of febrile seizure. After the second brief cluster of febrile seizure, we double-

checked for influenza virus with the RT-PCR test due to the low sensitivity of rapid influenza diagnostic test and high incidence of influenza patients in Korea during that season. The RT-PCR result was positive for the influenza virus so that we could diagnose the patient with influenza-associated AESD. This could suggest that clinicians should be aware of factors that can influence test results and of the limitations of available diagnostic tests.

There are no standard treatment guidelines worldwide for influenza-associated AESD. Various treatments for AESD have been suggested, such as intravenous immunoglobulin (IVIG) and methylprednisolone (MPD) pulse therapy. These treatments are effective in patients with other influenza encephalopathies like ANE and HSES by suppressing inflammatory cytokines. According to the studies of MPD pulse and IVIG therapies on ANE, seven patients without brainstem lesions had good outcomes with early steroid administration, while five had poor outcomes. The outcome was not correlated with IVIG use^{14,15}. However, the efficacy of MPD pulse therapy and IVIG in AESD has not yet been established. Antithrombin III, brain hypothermia, plasmapheresis, and cyclosporin A have also been recommended as treatments for AESD, but there is no evidence for these, either^{6,15}. In our case, we did not use oseltamivir because influenza-associated AESD was diagnosed after the symptoms subsided. We did not use IVIG or MPD pulse therapy due to the patient's spontaneous conscious improvement.

Because simple or complex febrile convulsions are common in influenza infection, doctors might fail to notice influenza-associated encephalopathy during seasons of influenza spread. Doctors should examine for neurologic complications of influenza infection in detail and should diagnose carefully. As we are the first to report the mild form of influenza-associated AESD in Korea, the ethnicity and regionality of influenza-associated AESD and other encephalopathy should be widely studied. Furthermore, the biological and genetic backgrounds and treatments of AESD should also be established.

요약

AESD는 3-4일의 간격을 두고 두 차례 열을 동반한 경련발작이 반복되며, MRI상 대뇌 피질 하 영역에 확산저하를 동반하는 특징적인 임상양상을 동반하는 질환이다. 인플루엔자 바이러스와 동반된 AESD는 2006년 첫 증례보고 이후로 일본에서는 최근 약 스무 명의 증례가 보고되었으나, 그 외의 나라에선 증례 보고가 매우 드물었다. 이 증례 보고는 한국에서 처음으로 보고되는 인플루엔자와 동반된 경한 AESD 증례이며, 이 보고를 바탕으로 인플루엔자를 동반한 AESD의 유전적

요인, 혹은 민족적 발병요인과 같은 폭 넓은 연구들이 필요할 것으로 보인다.

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