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Acute Encephalopathy With Biphasic Seizures and Late Reduced Diffusion Associated With Adenoviral Pneumonia

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Abstract

Acute encephalopathy with biphasic seizures and late reduced diffusion is a subtype of acute encephalopathy described in a cohort of Japanese children. Few cases have been reported in countries other than Japan. It is characterized clinically by biphasic seizures and late reduced subcortical diffusion on magnetic resonance imaging (MRI). We report the case of a 3-year-old Korean girl with acute encephalopathy with biphasic seizures and late reduced diffusion who presented with status epilepticus associated with fever and pneumonia. Human adenovirus was detected from a respiratory specimen using multiplex real-time reverse transcriptase polymerase chain reaction. After 5 days, she developed a second cluster of seizures followed by altered consciousness, aphasia, stereotypic movement, and developmental regression. Her brain MRI showed symmetrical and extensive restricted diffusion in the subcortical white matter, which finally resulted in global brain atrophy, consistent with acute encephalopathy with biphasic seizures and late reduced diffusion. Here, we report a case of acute encephalopathy with biphasic seizures and late reduced diffusion associated with preceding adenoviral pneumonia.

Keywords

acute febrile encephalopathy, adenovirus, seizures

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Acute encephalopathy with biphasic seizures and late reduced diffusion is a rare subtype of encephalopathy in children. It is characterized by prolonged febrile seizures, followed within a few days by a cluster of seizures, with altered consciousness and late symmetrical diffusion-restricted lesions in the subcortical white matter on brain magnetic resonance imaging (MRI).[1,2] Since Takanashi et al[3] determined the distinct clinicoradiological features of acute encephalopathy with biphasic seizures and late reduced diffusion in 2006, most cases have been reported in Japan. Most of these cases were associated with prodromal viral infections such as influenza virus A and B and human herpes virus-6 and -7.[2,3] Reports of acute encephalopathy with biphasic seizures and late reduced diffusion involving other ethnic groups are rare, as are those with concomitant adenovirus infection. Herein, we report the first Korean case of acute encephalopathy with biphasic seizures and late reduced diffusion in association with adenoviral pneumonia.

Case Report

A previously healthy 3-year-old Korean girl presented with generalized tonic–clonic seizures that started with focal impaired awareness with upward gaze deviation following a 5-day prodromal illness consisting of fever, cough, sputum production, and rhinorrhea. She received prompt treatment

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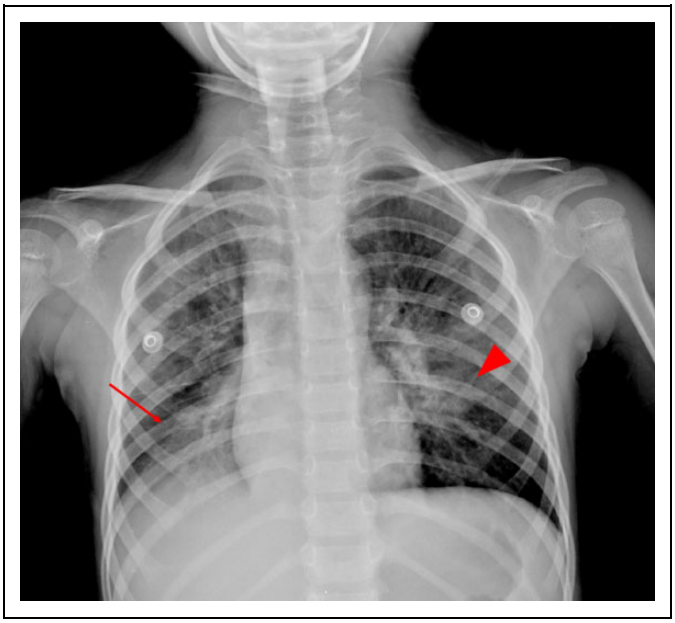

Figure 1. Chest radiograph showing pneumonic consolidation in the right lower lung field (arrow) and haziness around the wall of the left bronchus (arrowhead).

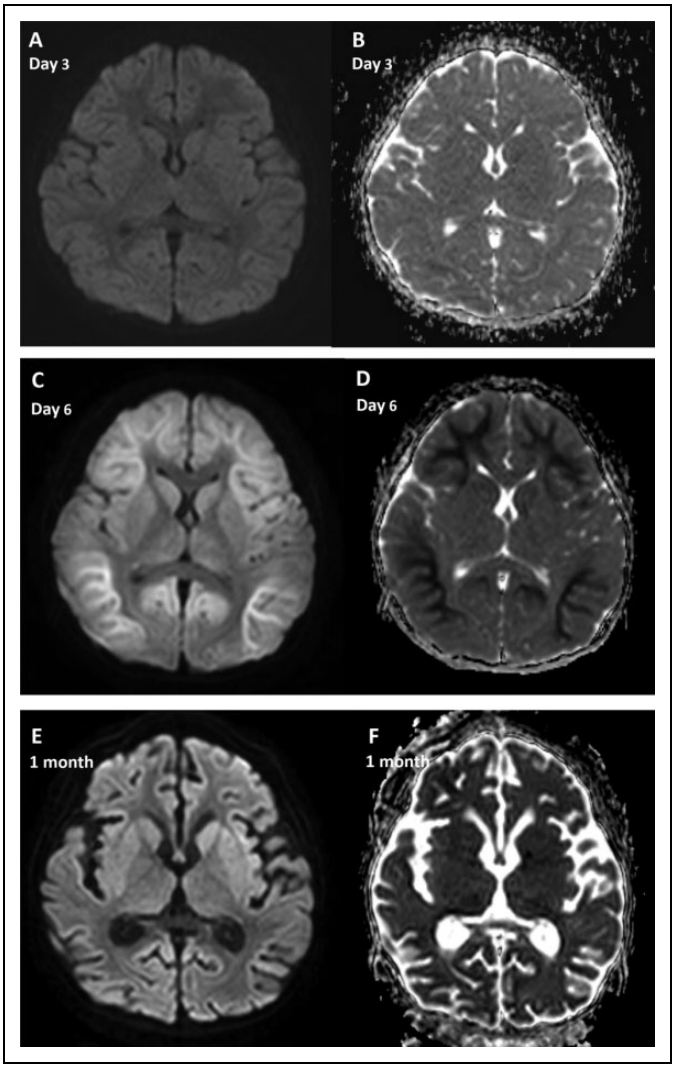

Figure 2. Initial brain magnetic resonance diffusion-weighted images (A) and apparent diffusion coefficient map (B) obtained on day 3 of hospitalization showed no definite abnormality involving the cerebral hemispheres. Repeated diffusion-weighted imaging (C) and apparent diffusion coefficient map (D) on day 6 of hospitalization revealed symmetrical diffusion restriction involving the subcortical white matter bilaterally, with sparing of the perirolandic area. Follow-up diffusion-weighted imaging (E) and apparent diffusion coefficient map (F) obtained 1 month later showed diffuse and extensive cerebral atrophy.

with intravenous diazepam in a local hospital's emergency department. Thereafter, she was transferred to our center as her seizures lasted more than 90 minutes. Upon arrival at our emergency department, she exhibited rigidity of the upper and lower extremities, with upward deviation of her gaze. Her symptoms were refractory to typical doses of benzodiazepines but were subsequently controlled with a bolus of intravenous phenobarbital (15 mg/kg/dose). Her temperature on admission was 38.5°C. Auscultation of both lung fields demonstrated bilateral crackles. Her chest radiograph showed pneumonic consolidation of the right lower lung and a patchy density around the wall of the left bronchus (Figure 1). Her initial blood, urine, and cerebrospinal fluid analyses revealed no abnormality, except for an elevated serum C-reactive protein (2.01 mg/dL; reference range, <0.5 mg/dL). Blood, urine, and cerebrospinal fluid cultures showed no growth, and cerebrospinal fluid polymerase chain reaction (PCR) for enterovirus, herpes simplex virus type 1 and 2, varicella zoster virus, cytomegalovirus, measles, human herpes virus-6, and adenovirus was negative. However, multiplex real-time reverse transcriptase PCR assay for respiratory viruses from a nasopharyngeal aspirate was positive for human adenovirus. Although she did not revert to her baseline mental state, her condition improved on day 3 after admission, whereby she could sit unassisted and talk to her parents. Brain MRI with diffusion-weighted imaging and electroencephalography (EEG) showed no abnormality on day 3 of hospitalization (Figure 2A and B). However, her serum C-reactive protein increased to 11.12 mg/dL, and her fever and respiratory symptoms persisted. We presumed that she had prolonged febrile seizures provoked by adenoviral pneumonia. On day 6 of hospitalization, she developed clustering focal clonic seizures characterized by eye blinking, facial twitching, and clonic movement of the right lower limb, which were terminated with a bolus administration of intravenous phenytoin (15 mg/kg/dose). A second awake and sleep EEG showed diffused high-voltage slow waves without reactivity, sleep spindles, or vertex sharp transients. Follow-up brain MRI with diffusion-weighted imaging (day 6) showed newly developed diffused cortical swelling in the cerebral hemispheres and symmetrical restricted diffusion in both subcortical white matter, with sparing of the perirolandic area (Figure 2C and D). She demonstrated postictal drowsiness, aphasia, intermittent myoclonus, stereotypic movement of hand rubbing and biting, and severe motor and verbal regression. She could not sit

unassisted, say any meaningful word, or make eye contact. Intravenous methylprednisolone pulse therapy (30 mg/kg/d for 5 consecutive days) and immunoglobulin (2 g/kg) were administered. A follow-up brain MRI obtained 2 weeks after admission showed that the previous diffusion restricted lesions had normalized. Approximately 1 month later, she regained her gross motor functions. However, her brain MRI showed diffused atrophic changes involving both cerebral hemispheres (Figure 2E and F). She could walk unassisted and run but could not utter any meaningful word. Assessments with the Sequenced Language Scale for Infants and Korean-Child Development Inventory revealed that all developmental domains, including gross and fine motor, language, cognition, social, and adaptive behavior, were severely delayed. Her developmental age equivalent of receptive and expressive language was only 1 month, and her integrated developmental age was 11 months. One year later, she still showed psychomotor developmental regression, with diffused parenchymal atrophy without any interval change on brain MRI.

Discussion

The clinical features of our patient were consistent with acute encephalopathy with biphasic seizures and late reduced diffusion. The initial neurologic symptom of our patient was a prolonged febrile seizure. Although the initial brain MRI and EEG were normal, and her mental state recovered transiently, she developed secondary seizures followed by worsening consciousness, aphasia, and stereotypic movements. Repeated MRI studies revealed symmetrical restricted diffusion of the subcortical white matter bilaterally with sparing of the perirolandic region, and cortical swelling involving both cerebral hemispheres, which culminated in diffused brain atrophy 1 month later. The radiological features and absence of cerebrospinal fluid pleocytosis in this case were also compatible with acute encephalopathy with biphasic seizures and late reduced diffusion.

Influenza virus or human herpes virus-6 and -7 are the main preceding infections in over half of acute encephalopathy with biphasic seizures and late reduced diffusion cases.[1,3] To our knowledge, only one case of acute encephalopathy with biphasic seizures and late reduced diffusion in association with adenovirus has been previously reported.[3] Adenoviruses are common pathogens that typically cause mild infections involving the respiratory tract, gastrointestinal tract, or conjunctiva in infants. These occur mainly due to the infants' lack of humoral immunity.[4] Although uncommon, adenovirus can cause central nervous system dysfunction, the most common of which is febrile or afebrile seizures, followed by encephalitis, cerebellitis, and acute disseminated encephalomyelitis.[5] We suspected acute encephalopathy with biphasic seizures and late reduced diffusion associated with adenoviral pneumonia based on clinicoradiological correlation and detection of adenovirus using multiplex PCR. However, the virus was detected from a nasopharyngeal aspirate and not the cerebrospinal fluid. Nevertheless, in many reports, the diagnosis of adenovirus encephalitis was not based on a positive cerebrospinal fluid result, but rather on the detection of the virus from other sites (nasopharynx, throat, or sputum) in patients with neurological symptoms.[5,6] This suggests that the central nervous system dysfunction may not require direct viral invasion.[7] In the present case, prolonged seizures and excitotoxic neuronal damage may be related to the acute encephalopathy with biphasic seizures and late reduced diffusion pathogenesis.[1,3] Although the definite mechanism of acute encephalopathy with biphasic seizures and late reduced diffusion remains unknown, previous magnetic resonance spectroscopy demonstrated elevated glutamine/glutamate complex in the acute state.[1] Excessive binding of glutamate to the N-methyl-D-aspartate (NMDA) receptors may allow an excessive influx of calcium into the postsynaptic neuron, causing delayed neuronal apoptosis shown by diffusion-restricted lesions on MRI.[1,3] Inflammatory cytokines provoked by adenovirus may also induce excitotoxicity in the brain, resulting in neuron death.[3]

The neurodevelopmental outcome is not good considering that over half of children with acute encephalopathy with biphasic seizures and late reduced diffusion had epilepsy, hemiparesis, spastic quadriplegia, or severe cognitive and motor impairment.[1,8] Poor outcomes are related to prolonged seizures at the onset and decreased consciousness 24 hours after onset, which explains the poor prognosis of our patient.

We report what is, to our knowledge, the first case of a Korean child presenting with acute encephalopathy with biphasic seizures and late reduced diffusion associated with adenoviral pneumonia. Acute encephalopathy with biphasic seizures and late reduced diffusion is rarely reported outside of Japan; only 3 children, one each in Turkey, India, and United States, have been reported thus far.[7,9,10] Furthermore, the American patient was a Japanese infant residing there, indicating a possible underlying genetic background related to the development of acute encephalopathy with biphasic seizures and late reduced diffusion.[3,7] However, many cases with acute encephalopathy with biphasic seizures and late reduced diffusion might be missed because MRI abnormality is not seen for a few days. Therefore, pediatric neurologists and radiologists should be aware of the clinicoradiologic features of acute encephalopathy and perform brain MRI in patients suspected of having acute encephalopathy with biphasic seizures and late reduced diffusion, to detect the dynamic MRI changes.

In conclusion, the diagnosis of acute encephalopathy with biphasic seizures and late reduced diffusion is based on the presence of biphasic seizures and distinctive imaging features. Brain MRI with diffusion-weighted imaging is an essential tool to detect this type of encephalopathy in a patient with febrile status epilepticus who is showing repetitive seizures or neurologic deterioration. Additionally, adenovirus should also be considered as a preceding pathogen of acute encephalopathy with biphasic seizures and late reduced diffusion.

Authors' Note

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Author Contributions

BLL and KSL contributed to diagnoses and management, collected data, wrote, and reviewed the manuscript. YJH contributed to diagnoses and reviewed the manuscript. All authors read and approved the final manuscript.

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Ethical Approval

On behalf of all authors I certify that the work submitted is original, has not been plagiarized, and has not been published anywhere else. We have no conflicts of interest to report.

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