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Case report

Acute Focal Bacterial Nephritis Characterized by Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion

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ABSTRACT

Acute focal bacterial nephritis (AFBN) is a localized bacterial infection of the kidney presenting as an inflammatory mass, and some patients show deterioration of clinical condition with neurological symptoms. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a syndrome that is characterized by biphasic seizures and impaired consciousness with reduced diffusion in the subcortical white matter on magnetic resonance imaging, typically observed between days 3 and 9 after clinical onset. Although AFBN sometimes causes neurological symptoms, no cases of AFBN with AESD have been reported, and no studies have presented the cytokine profiles of patients with a severe form of acute encephalopathy with AFBN. We report here a very rare case involving a 6-month-old boy who developed AFBN due to *Enterococcus faecalis* with both the clinical and radiological features of AESD. In our patient, serum interleukin (IL)-6, IL-10, and interferon (IFN)-γ levels markedly increased on admission, and on day 4, only IL-6 levels significantly increased in the cerebrospinal fluid (CSF). These results suggest that high serum cytokines are produced locally in response to AFBN and elevated IL-6 levels in CSF may have neuroprotective roles.

Key words: acute encephalopathy with biphasic seizures and late reduced diffusion; acute focal bacterial nephritis; cytokines; *Enterococcus faecalis*; pediatrics

INTRODUCTION

Acute focal bacterial nephritis (AFBN) is a localized bacterial infection of the kidney presenting as an inflammatory mass without abscess formation. The symptoms include fever, vomiting, and flank or abdominal pain; some patients show rapid deterioration of clinical condition with neurological symptoms[1-3].

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a syndrome characterized by biphasic seizures and impaired consciousness. These symptoms are followed by reduced diffusion in the subcortical white matter on magnetic resonance imaging (MRI), which presents as a 'bright tree appearance' typically observed between days 3 and 9 after clinical onset[4,5]. The outcome of patients with AESD varies from normal to severe mental retardation, paralysis, and epilepsy, and the mortality rate is relatively low (<5%)[6].

Although AFBN sometimes causes neurological symptoms[3,7], and a case with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) associated with AFBN has already been reported[7], no cases of AFBN with AESD have been reported. Additionally, although some studies have investigated the characteristics of the cytokine profiles in patients with AFBN[2,7,8], none have shown the serial cytokine profiles of patients with a severe form of acute encephalopathy.

Here, we report a case in which a 6-month-old Japanese boy developed AFBN due to *Enterococcus faecalis* with both the clinical and radiological features of AESD. Notably, this is apparently the first reported case describing the inflammatory profile of AFBN characterized by AESD.

CASE REPORT

A previously healthy 6-month-old boy presented to a hospital with febrile generalized tonic-clonic convulsions lasting 40 min. After buccal midazolam administration, he was intubated because of deterioration in respiratory status. After blood and urine culture were performed, cefotaxime was administered and he was transferred to our hospital. On admission, continuous electroencephalography (EEG) monitoring and head computed tomography (CT) revealed no abnormalities. As he opened his eyes and began moving his extremities, he was extubated 7 hours after admission. His consciousness rapidly improved to Glasgow Coma Scale (GCS) 15 after extubation. However, his fever continued, and he was irritable and showed decreased appetite. Four days after admission, his mental state suddenly deteriorated from GCS15 to GCS3 with convulsions in the left extremities. These convulsions resolved within one minute without medication. However, he continued to cry and was irritable. An hour later,

convulsions occurred in his left extremities and face and his eyes deviated to the right. Continuous EEG monitoring showed rhythmic, diffuse high-voltage slow activity. These seizures were finally controlled with administration of intravenous midazolam and fos-phenytoin after 7 min. We could not confirm his diagnosis based on these symptoms. However, abdominal ultrasound and enhanced abdominal CT indicated AFBN (Fig. 1). Vancomycin was administered in addition to cefotaxime. On the same day, we performed a head MRI, which revealed a bright tree appearance in the right subcortical areas (Fig. 2 (A)). Results of cerebrospinal fluid (CSF) analysis were normal, and CSF culture was negative. After vancomycin was added, his consciousness gradually improved to GCS15 on day 5. Seven days after admission, his blood culture was negative; however, urine culture from the previous hospital was positive for *E. faecalis*. Therefore, he was diagnosed with AESD concomitant with AFBN due to *E. faecalis*. Based on antimicrobial susceptibility tests, the antibiotics were changed to intravenous ampicillin, which was then changed to oral amoxicillin and continued for a total of 21 days. On the 16th day, the head MRI showed subdural effusion, although the bright tree appearance diminished (Fig. 2 (B)). In addition, we measured the transitional change of serum inflammatory markers (Table. 1). The serum concentrations of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were measured using a BD™ Cytometric Bead Array Human Th1/Th2 Cytokine Kit II (BD Biosciences, San Jose, CA, USA). Serum IL-6 and IFN -γ were markedly increased on admission, which then gradually decreased. However, in the CSF, only IL-6 significantly increased on day 4. He had a sequela of left incomplete hemiparesis. He was discharged 20 days after admission and returned for a follow-up visit and MRI 60 days after admission. His MRI showed persisting right subdural effusion and brain atrophy (Fig. 2 (C)). This case was reported to the regional public health center.

DISCUSSION

The present case of AFBN followed a clinical course that included biphasic seizures and worsening consciousness, as has been described for AESD. Furthermore, MRI performed on day 4 showed reduced diffusion, which is characteristic of AESD. Given these similarities, he was diagnosed with AFBN concomitant with AESD. Although viral infections have been reported as the main etiology of AESD[5], we have previously reported a case associated with bacteremia[9]. To the best of our knowledge, our present case is the first involving AESD with AFBN. AESD may occur after prolonged febrile seizures caused by not only viral but also various bacterial infections.

Two challenges associated with AFBN were encountered in the present case. First,

AFBN is often difficult to diagnose because it can only be established using imaging tests, such as abdominal ultrasound or enhanced CT. Second, the cause of AFBN was *E. faecalis,* which is generally cephalosporin-resistant, although cefotaxime is often used as a broad-spectrum antibiotic for fever of unknown origin. In fact, the fever had sustained for 5 days after admission. However, after adding vancomycin (trough value of serum concentration two days after initiation was 13.6 μg/ml), the fever conditions were immediately restored to normal. In addition, we re-performed abdominal ultrasound, and confirmed that the findings characteristic of AFBN had disappeared. Therefore, vancomycin was considered effective.

Sieger et al. reported that the most frequent pathogen is *Escherichia coli*, as it was detected in 83% of all positive urine cultures. Sporadically, other gram negative bacteria have also been reported[10]. However, recently, some studies on neurological disturbance caused by AFBN have been reported[3,7]. Therefore, if clinicians are presented with a patient with a fever of unknown origin with neurological disturbance, abdominal imaging should be performed. Moreover, gram staining will help identify the presence of *Enterococcus* spp, thus aiding the administration of the appropriate antibiotics.

Although the pathomechanism of AESD remains unclear, a prolonged seizure may trigger excitotoxicity, causing delayed neuronal death. Takanashi et al. proposed that prolonged overactivation of epileptic neurons leads to increased levels of glutamate in patients with AESD[11]. They speculate that such elevations may be explained by a dysfunction of astrocytes, which play an important role in the regulation of extracellular glutamate levels, and excessive glutamate may allow a massive influx of calcium into postsynaptic neurons, causing delayed neuronal death. The main pathophysiology of our patient may be excitotoxicity because he had a prolonged seizure lasting 40 min.

Some studies have reported inflammatory responses in AFBN and have shown higher serum levels of IFN-γ, IL-6, IL-10, and soluble TNF-receptor 1 (sTNFR1) or an increase in some of these[2,7,8]. Our results are compatible with these results as our patient showed markedly increased serum IL-6, IL-10, and IFN-γ levels on admission, which then gradually decreased. However, in the CSF, only IL-6 significantly increased on day 4. Ichiyama et al. reported the presence of cytokines in the serum and CSF in acute encephalopathy following prolonged febrile seizures (AEPFS)[12]. They showed that serum IL-6, IL-10, sTNFR1, and CSF IL-6 were significantly higher in AEPFS patients. They explained that the increased serum cytokine levels may be due to inflammation in the blood of patients with AEPFS and the elevated CSF IL-6 levels may play a protective role against the excitotoxic damaged brain tissue. Therefore, the

high levels of serum IL-6, IL-10, and INF-γ in our patient may be due to severe inflammatory damage of the kidney because these levels seemed to be higher than that reported previously[2,7,8].

In conclusion, we describe a case of AFBN due to *E. faecalis* with both clinical and radiological features of AESD. Further studies will be required to determine the exact relationship between bacterial infection and AESD.

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Declaration of Conflict of Interests

The authors declare no potential conflicts of interest and received no financial support.

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Figure 1.

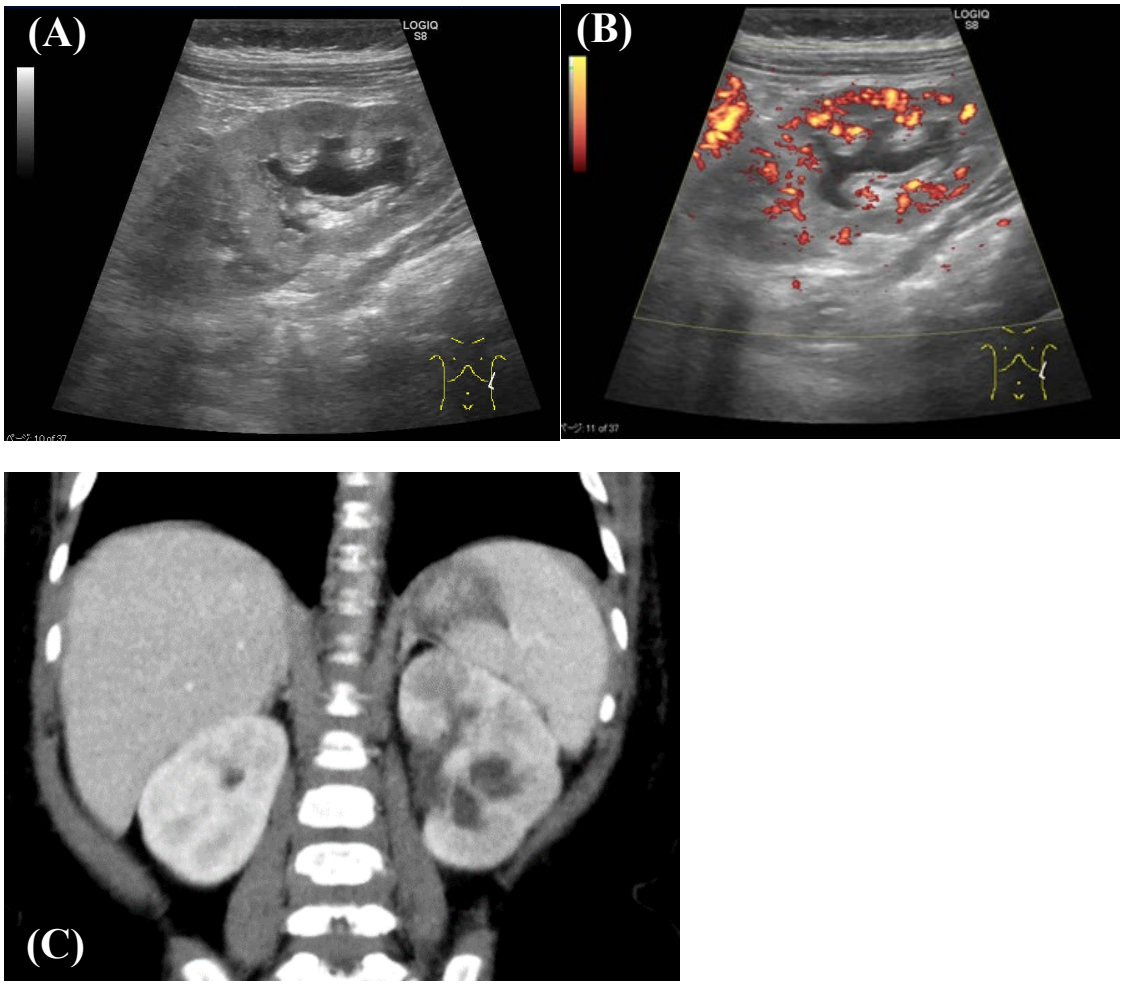

Figure 2.

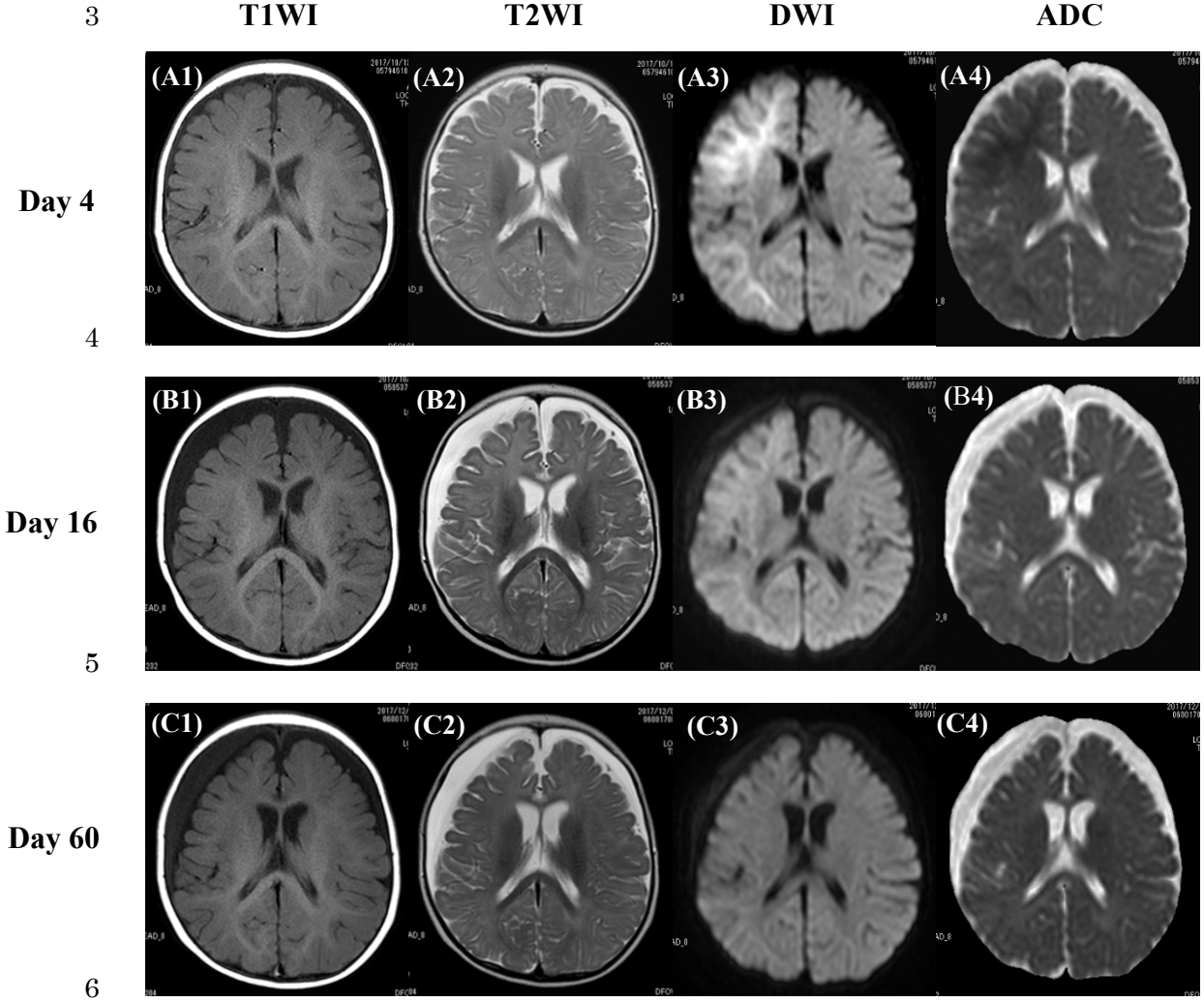

Figure legends

Figure 1. Ultrasound images of left kidney (A,B) and enhanced abdominal CT (C) of the patient. Ultrasound of left kidney showed pelvicalyceal dilation, a swollen upper side, poorly marginated cortico-medullary junction (A), and decreased blood flow (B). Enhanced abdominal CT showed enlargement of the left kidney with a mass lesion on the upper side (C).

Figure 2. Serial cranial MRI findings (A1-C4) on admission, left to right column: T1-weighted images (T1WI), T2-weighted images (T2WI), diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) map at the basal ganglia-thalamus level, obtained on (top to bottom rows) day 4, 16, and 60. DWI image on day 4 shows

reduced diffusion in the right subcortical white matter with perirolandic sparing, and reduced diffusion in the corresponding subcortical matter is verified on the ADC map (A4). Although the high-intensity lesions became less apparent (B3), right side-dominant subdural edema appeared (B2) on day 16. Slight brain atrophy was observed on day 60 (C).

Table 1. Laboratory data of the patient

	Normal range	Day1	Day3	Day4	Day6	Day17
Complete blood cell counts						
WBC (/μL)	**(4,400-19,100)**	**8,800**				
Hb (g/dL)	**(10.0-14.2)**	**12.7**				
Plt ($\times 10^4$/μL)	**(22-76)**	**19**				
Chemistry						
Na (mEq/L)	**(135-143)**	**137**				
K (mEq/L)	**(4.0-5.4)**	**3.9**				
Cl (mEq/L)	**(101-110)**	**107**				
AST (U/L)	**(25-68)**	**41**				
ALT (U/L)	**(13-55)**	**22**				
CRP (mg/dL)	**(0-0.14)**	**6.12**				
GLU (mg/dL)	**(73-109)**	**192**				
Cytokine profile						
Serum (pg/mL)						
IL-2	**(< 3.9)**	**3.73**	**5.81**		**4.96**	**3.79**
IL-4	**(< 3.8)**	**2.6**	**9.99**		**9.22**	**8.17**
IL-6	**(< 9.5)**	**1047.35**	**29.16**		**19.87**	**8.02**
IL-10	**(< 6.8)**	**42.53**	**5.72**		**7.73**	**7.18**
IFN-γ	**(< 21.1)**	**538.39**	**35.31**		**20.66**	**16.33**
TNF-α	**(< 3.9)**	**9.43**	**4.66**		**< 2.8**	**3.67**
CSF (pg/mL)						
IL-2	**(< 2.6)**			**3.2**		
IL-4	**(< 6.6)**			**3.6**		
IL-6	**(< 6.2)**			**56.8**		
IL-10	**(< 2.8)**			**3.5**		
IFN-γ	**(< 7.1)**			**13.2**		
TNF-α	**(< 3.5)**			**6.2**		

Abbreviation: WBC, white blood cells; Hb, Hemoglobin; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; CSF, cerebrospinal fluid; GLU, glucose; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor