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Original article

Prediction of acute encephalopathy with biphasic seizures and late reduced diffusion in patients with febrile status epilepticus

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Abstract

Introduction: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common subtype of acute encephalopathy among children in Japan. The pathogenesis of AESD is mostly delayed cerebral edema caused by excitotoxic injury. It is difficult to discriminate AESD and complex febrile seizure in the early phase. Many cases have neurologic sequelae because early intervention is difficult.

Methods: To establish an early diagnostic method, we assessed 213 hospitalized cases of febrile status epilepticus (FSE) between January 2004 and August 2014. We categorized FSE cases into an AESD group and a non-AESD group and compared their clinical courses, laboratory data and cranial computed tomography (CT) findings.

Results: Of 213 hospitalized FSE cases, 19 (9%) were AESD. Univariate analysis showed that the AESD group took a significantly longer time to wake after FSE, had a higher degree of respiratory acidemia, and higher levels of serum AST, ALT, LD, hyperglycemia and hyperammonemia than the non-AESD group. We developed a scoring model that predicts AESD based on multivariate analysis. Using cut-off points of 4 and more with this scoring model, we could identify the AESD cases with 93% sensitivity and 91% specificity. These scores also had a positive correlation with prognosis.

Discussion: Our scoring model enables early diagnosis of AESD. Patients with high scores should be observed carefully and early intervention should be considered.

Keywords: Acute encephalopathy; Biphasic; Diffusion MRI; Complex febrile seizures; Status epilepticus; Brain hypothermia

1. Introduction

Acute encephalopathy affects 400–700 children per year in Japan, and AESD is the most common subtype of acute encephalopathy, accounting for about 30% of all cases [1]. AESD has been reported as a new type of acute encephalopathy since the 1990s [2]. An overwhelming number of AESD cases occur in Japan, and most of the reports are from Japan. Typical AESD is characterized by FSE on the first day, followed by a transient recovery of consciousness. The secondary cluster of complex seizures occurs on days 3–6, with magnetic resonance imaging (MRI) showing a reduced

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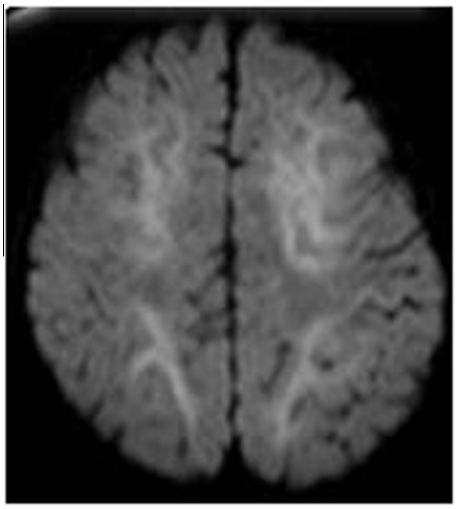

Fig. 1. Axial diffusion-weighted image shows high-intensity lesion in the subcortical white matter. AESD is characterized by this lesion.

diffusion in the subcortical white matter, or a "bright tree" appearance (BTA; Fig. 1). Affected children have various levels of neurological sequelae [3,4].

It has been difficult to discriminate AESD and complex febrile seizure in the early phase, because both symptoms begin with FSE followed by a transient recovery of consciousness. And most cases have been treated after secondary seizures and under pathognomonic MRI findings. The pathogenic mechanism underlying AESD is mostly tied to excitotoxic injury. But an early diagnosis is still difficult, because no useful biomarker has been established. Furthermore, effective treatments have not been established, and many cases are not able to avoid neurological sequelae.

In this report, we categorized FSE cases into an AESD group and non-AESD group and compared their clinical courses, laboratory data and cranial CT findings at the first medical examination to identify reliable clues for early diagnosis.

2. Study design

A retrospective research by a single institution.

3. Patients

We reviewed the cases of Japanese children younger than 16 years old with FSE who were treated in our institution from January 2004 to August 2014. We excluded children with acute encephalopathy other than AESD and acute encephalitis. We defined a febrile seizure as a seizure with fever (>38.0 °C), and FSE as a visible seizure lasting for >30 min. Although some cases of AESD start with afebrile seizures, do not develop FSE or follow a biphasic course, we defined AESD based on the following criteria:

(1) febrile seizure develops to FSE;
(2) consciousness recovers during acute period except for children who have been continuously sedated;
(3) secondary seizures or disturbance of consciousness appears 3–6 days later; and
(4) diffusion-weighted MR images show BTA at secondary phase.

4. Methods

We categorized FSE cases into an AESD group and a non-AESD group and compared their age (months) at onset, clinical course (seizure duration, time until waking, and number of drugs administrated for seizure), laboratory data and cranial CT findings. These data were accessed retrospectively using medical records.

We selected a set of laboratory data that can be measured in any institution and has a short analysis time. Assuming that cases developing encephalopathy have severe seizure and a high degree of acidemia, and involve various organs, we used potential hydrogen (pH) levels, mixed venous partial pressure of CO_2 ($PvCO_2$) levels, serum lactic acid levels, serum aspartate transaminase (AST) levels, serum alanine transaminase (ALT) levels, serum lactate dehydrogenase (LD) levels, serum creatinine (Cr) levels, serum sodium levels, platelet count, blood glucose levels, and serum ammonia (NH_3) levels. We recorded seizure duration every 5 min and truncated any fraction less than 5 min.

We recorded time until waking every 0.5 h from the last dose of anticonvulsive drugs and truncated any fraction less than 0.5 h.

We defined waking as Glasgow coma scale (GCS) > 14. We recorded the laboratory data when the patients just arrived at the institution, so all data were during seizure or immediately after seizure.

If the seizure continued after patients had arrived at the institution, we expeditiously secured an intravenous catheter and administered diazepam (DZP) (0.3–0.5 mg/kg/dose) in most cases. If DZP was not effective, we next tried midazolam (MDL) (0.3 mg/kg) and then thiamylal (THA) (3 mg/kg). The interval between administration of each drug (the time given to observe its effects) was 1–5 min.

We performed cranial CT immediately after the seizure had calmed down. We evaluated the neurodevelopmental outcome of AESD using the pediatric cerebral performance category (PCPC) scale [5] at 6–12 months after the treatment, except for in cases that had underlying diseases affecting the score (Table 1).

After visual inspection of variables, we employed the Mann–Whitney U nonparametric test to compare variables between the two groups, with the goal of developing a medical test for predicting AESD. Based on the results from univariate analyses described above, we