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Predictive score for early diagnosis of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)

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ABSTRACT

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) at onset manifests an early seizure (ES) usually lasting more than 30 min. Following ES, some patients exhibit almost clear consciousness with no neurological symptoms, and no MRI abnormality for a few days, which may lead to an initial misdiagnosis of prolonged febrile seizures (PFS). To allow an early diagnosis of AESD, we retrospectively analyzed clinical manifestations, laboratory data, and radiologic and EEG findings in patients with AESD ($n = 62$) having ES of over 30 min, and ones with PFS ($n = 54$), using logistic regression analyses. Multivariate logistic regression analysis revealed that an age below 1.5 years and a Glasgow Coma Scale score of 14 or less than 14 (Japan Coma Scale score of 1 or higher) were high risk factors of developing AESD. We proposed an AESD prediction score system consisting of consciousness level, age, duration of convulsions, enforcement of mechanical intubation, and aspartate aminotransferase, blood glucose and creatinine levels (full score: 9), the mean scores in AESD and PFS being 5.9 and 1.8, which were significantly different ($p < 0.001$). We herein propose a scoring system for differentiating patients with AESD and PFS around the time of ES (score of 4 or more than 4 suggesting AESD), which may contribute to early therapeutic intervention and an improved neurologic outcome.

1. Introduction

Acute encephalopathy is a generic term for acute brain dysfunction caused by various agents, such as infection, metabolic disease, hepatic or renal dysfunction, and hypertension. The pathologic substrate of acute encephalopathy is diffuse or widespread, non-inflammatory brain edema. Thus, inflammatory cells are not usually found in the brain or cerebrospinal fluid (CSF), as included in the diagnostic criteria for acute necrotizing encephalopathy (ANE) [1]. In Japan, acute encephalopathy is usually associated with infection, most often by influenza virus or human herpes virus (HHV) 6 and 7, and its incidence is highest in infancy and early childhood [1–3]. The diagnosis is easy for patients with acute necrotizing encephalopathy (ANE), and hemorrhagic shock and encephalopathy syndrome (HSES), because they usually present monophasic, progressive consciousness disturbance. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common subtype of acute para-infectious encephalopathy in Japan, accounting for around 30% of patients (120–200 per year) [2]. AESD is clinically characterized by a febrile seizure usually lasting

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ALT, alanine aminotransferase; ANE, acute necrotizing encephalopathy; AST, aspartate aminotransferase; BS, blood sugar; BTA, bright tree appearance; Cr, creatinine; CSF, cerebrospinal fluid; DWI, diffusion weighted imaging, EEG, electroencephalography; ES, early seizure; GCS, Glasgow Coma Scale; HSES, hemorrhagic shock and encephalopathy syndrome; IL, interleukin; JCS, Japan Coma Scale; LDH, lactate dehydrogenase; LS, late seizures; MMP, matrix metalloproteinase; PFS, prolonged febrile seizures; TIMP, tissue inhibitor of metalloproteinase 1.

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more than 30 min (early seizure [ES]) as the initial neurological symptom on day 1, followed by late seizures (LS), most often a cluster of complex partial seizures, associated with deterioration of the consciousness level on days 4 to 6, and mild to severe neurologic sequelae. MRI findings are typically normal on day 1 or 2, followed by a subcortical white matter lesion (bright tree appearance [BTA]), most obvious in diffusion weighted imaging (DWI), on days 3–9. Between the biphasic seizures, some patients exhibit continuous disturbance of the consciousness level, leading to an early diagnosis of encephalopathy and the initiation of therapy; but other patients (around 20–30%) exhibit normal to minimally disturbed consciousness with no neurological symptoms [3]. Clear consciousness and normal MRI after ES in AESD may lead to an initial misdiagnosis of prolonged febrile seizures (PFS), and a delay of therapeutic intervention for encephalopathy.

Therefore, we attempted to identify clinical, laboratory, neuroradiological and electroencephalography (EEG) findings useful for differentiating AESD from PFS in the acute stage, and also to develop a scoring system for predicting AESD.

2. Patients and methods

A questionnaire was sent to members of the Committee for Research on the Etiology, Diagnosis and Treatment of Severe and Intractable Acute Encephalopathy, Japan, and to some members of the Annual Zao Conference on Pediatric Neurology after institutional review board approval from the Kameda Medical Center. The diagnosis of AESD was based on the previously reported diagnostic criteria with modification [2] (Table 1). In this study, we evaluated AESD patients with ES lasting longer than 30 min. When MRI showed BTA, a diagnosis of AESD was made even if the patient lacked LS, because strong medication (such as pentobarbital) under intubation with a muscle relaxant may mask LS. PFS were defined as FS lasting longer than 30 min with a good prognosis, no LS, and no MRI lesions. The data for patients with PFS were collected from the Kameda Medical Center. The onset of fever was defined as day 1. Various clinical and laboratory data, and neuroradiological and EEG findings at the acute stage of the illness (prior to LS) were statistically analyzed (Table 2). The consciousness level was evaluated using the Glasgow Coma Scale (GCS) and Japan Coma Scale (JCS) at 12–24 h after ES. JCS is most often used to evaluate the consciousness level in Japan, with which consciousness is divided into 10 levels (JCS 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300), ranging from clear consciousness (JCS 0) to deep coma (JCS 300) [4]. A close correlation has been reported between the GCS and JCS scores; GCS 15 is equivalent to JCS 0, GCS 14–13 to JCS 1–3, GCS 12–9 to JCS10–30, and GCS 8–3 to JCS 100–300 [5]. Univariate logistic regression analysis was performed in AESD and PFS patients, and the variables showing a significant difference were subjected to multivariate logistic regression analysis. The threshold was determined from the ROC curve for all variables showing a significant difference on univariate logistic regression analysis, and a scoring system for the early diagnosis of AESD was developed using these variables. Scores were based on the regression coefficients and point estimations of the variables. Fisher's test was used to confirm whether or not this scoring system effectively differentiates AESD and PFS. Statistical analysis was performed using SAS 9.3, and a p value < 0.05 was taken to indicate significance.

Table 1
Diagnostic criteria for AESD.

1. Onset with convulsions (status epilepticus convulsions in most cases) within 24 h from the onset of fever
2. Subsequent, transient improvement in consciousness
3. Recurrence of convulsions (clustered partial seizures in most cases) on fourth to sixth day of illness, followed by impairment of consciousness
4. Pathogens of infection: influenza virus and HHV-6, 7 in many cases
5. Normal MRI on first to second day of illness
6. High signal intensity lesions in cerebral subcortical white matter on diffusion-weighted imaging on third to ninth day of illness. T2-weighted and FLAIR images may show high signal intensity along U-fibers
7. Exclusion of resembling diseases, including ADEM, HHE, vasculitis and metabolism abnormality with white matter abnormality.

Table 2
Variables compared between AESD and PFS patients.

1. Patient characteristics: age, male/female, past history of febrile seizures, family history of febrile seizures, antipyretics before onset, pathogens
2. Clinical factors: onset day of early seizures, duration of seizures, laterality of seizures, maximum body temperature (°C), consciousness level 12–24 h after seizures, mechanical ventilation
3. Laboratory data: WBC, Hb, PLT, AST, ALT, LDH, AESD index: AST × LDH/ALT, CK, UN, Cr, blood glucose, sodium, K, Cl, PT, APTT, PH, PCO_2, BE and CSF (cell, protein and glucose), cytokines (IL-6 and TNF-α), lactic acid on admission
4. Brain CT around early seizures
5. Brain MRI around early seizures
6. EEG around early seizures

3. Results

3.1. Patient characteristics

62 AESD patients with ES lasting longer than 30 min (31 males and 31 females) and 54 PFS patients (27 males and 27 females) were enrolled in this study. The pathogen of infection was identified in 39 (62.9%) of the 62 patients with AESD; human herpes virus (HHV)-6 in 24 (38.7%), influenza virus A or B in 6 (9.7%), respiratory syncytial (RS) virus in 3 (4.8%), rota virus in 2 (3.2%), and other pathogens in 4 (6.5%).

3.2. Statistical analysis of clinical course, laboratory data, MRI, CT, and EEG

Univariate logistic regression analysis was performed for all variables shown in Table 2. Because data on cytokines, such as interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and lactate, were available only in a small number of patients (less than 10 patients with AESD), these variables were excluded from the statistical analysis. Univariate logistic regression analysis showed that age, duration of ES, consciousness level at 12–24 h after ES, presence or absence of intubation, abnormal EEG, and abnormal laboratory data, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), Na, creatinine (Cr), and blood sugar (BS) concentrations, were statistically significant variables indicating AESD relative to PFS ($p < 0.05$). The mean age of the 62 AESD patients was 1.7 years (range: 0.6–7.6 years), and that of the 54 PFS patients was 2.5 years (0.6–7.6 years). The median GCS was 9 (30 in JCS) in AESD, and 15 (0 in JCS) in PFS. The median and average ± SD of the duration of ES in AESD were 58 min and 65.5 ± 48.8 min, and those in PFS 35 min and 48.5 ± 24.3 min. Intubation was performed in 26/62 patients with AESD, and in 2/54 with PFS. The median and average ± SD of AST were 51 mEq/l and 81.7 ± 84.9 mEq/l in AESD, and 36 mEq/l and 37.7 ± 12.6 mEq/l in PFS. Those of Cr were 0.37 mg/dl and 0.37 ± 0.12 mg/dl in AESD, and 0.30 mg/dl and 0.31 ± 0.09 mg/dl in PFS. Those of BS were 230 mg/dl and 220 ± 91 mg/dl in AESD, and 129 mg/dl and 160 ± 57 mg/dl in PFS. EEG was abnormal in 26/34 patients with AESD and 7/26 patients with PFS, so examined. Multivariate logistic regression analysis revealed that an age below 1.5 years and a GCS score of 14 or less than 14 (JCS score of

Table 3
Regression coefficients and odds ratios of variables in which a significant difference was detected on univariate logistic regression analysis.

Prediction data	Odds ratio (95% CI)	*p* value	Regression coefficient
Age below 1.5 years	9.685 (1.970–47.610)	<0.005	2.271
GCS score of 14 or less than 14	233.26 (34.311–>999.999)	<0.001	5.452