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

Takaoki YOKOCHI[a], Takahito TAKEUCHI[a], Jumpei MUKAI[a], Yukihiro AKITA[a], Kojiro NAGAI[b], Keizo OBU[a], Tatsuyuki KAKUMA[c], and Toyojiro MATSUISHI[b*]

[a] Department of Pediatrics, St Mary's Hospital, Fukuoka, Japan

[b] Department of Pediatrics and Child Health Kurume University School of Medicine, Fukuoka, Japan

[c] Center for Bio-Statistics, Kurume University School of Medicine, Fukuoka, Japan

20 text pages and 4 figures

***Corresponding author:**

Toyojiro Matsuishi, M. D. ,PhD.

Department of Pediatrics and Child Health Kurume University School of Medicine, 67 Asahi-machi Kurume City, Fukuoka 830-0011, Japan

Tel: +81-942-31-7565, Fax: +81-942-38-1792;

E-mail: tmatsu@med. kurume-u. ac. jp

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 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 minutes. 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 used), 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 minutes and truncated any fraction less than 5 minutes.

We recorded time until waking every 0. 5 hours from the last dose of anticonvulsive drugs and truncated any fraction less than 0. 5 hours.

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.

We performed the 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 chose a set of clinical variables that were associated with AESD. We employed a multivariable logistic regression model to evaluate the effects of risk factors simultaneously. In order to develop a clinically sound medical test, we constructed a scoring rule based on the estimates and their standard errors based on the results of univariate logistic models. Then, we conducted a receiver-operator characteristic (ROC) curve analysis to decide an optimal cut-off point.

In addition, to investigate the availability of this predicting scoring model, we applied scores to other cases of encephalopathy and encephalitis that were excluded from the analysis.

We conducted Spearman's rank correlation coefficient analyses on AESD patients and all encephalopathy and encephalitis patients to test for associations between PCPC scores and our novel AESD predicting scores.

We performed all analysis using JMP Pro 11.2.1, and considered the probability value of < 0.05 to indicate statistical significance.

5. Results

5.1. Patients

During the study period, 223 cases met the criteria of FSE. Ten cases were excluded from analysis because of other acute encephalopathy or encephalitis. Of the 213 remaining cases were used for the analyses (Fig. 2). No patient repeated FSE in a single hospitalization period.

Of the 213 patients, 122 (57%) were males, and the median age at onset was 23 months, ranging from 3 to 168 months. Sixty-six (31%) had a past history of febrile seizure. Fifty-three (25%) had neurologic diseases: epilepsy in 27 cases, mental retardation in 28, cerebral palsy in 5, hydrocephalus in 4, Arnold-Chiari malformation in 2, cranioschisis in 1, hypoplasia of the corpus callosum in 3, low birth weight in 9, stroke in 1, encephalitis in 1, hypoxic ischemic encephalopathy in 4, congenital cytomegalovirus infection in 1, malformations of cortical development in 1, muscular dystrophy in 1, pervasive developmental disorder in 1, and chromosomal abnormality in 4, with some cases having more than one disease.

In 12 patients (6%), visible seizure had already stopped when they arrived at the institution. In 107 (50%), seizures were stopped by a single drug: diazepam (DZP) in 103 cases, and midazolam (MDL) in 4. In 58 (27%), seizures were stopped by two drugs: DZP + MDL in 54 and DZP + thiamylal in 4. For 35 patients (16%), seizures were stopped by three drugs: DZP + MDL + thiamylal in 34, and DZP + MDL + phenobarbital in 1. In 1 case, seizure was not stopped by three drugs.

5.2. The features of AESD

Of the 19 (9%) patients who were AESD (no repeated case), 8 (42%) were males. Of the 4 cases had neurologic diseases at the onset (hypoplasia of the corpus callosum and mental retardation in 1 case, mental retardation and epilepsy in 1, extremely low birth weight and mental retardation and epilepsy and stroke in 1, hypoplasia of the corpus callosum in 1).

The median time of the secondary seizures from onset 5 days, ranging between 3 and 6 days. The consciousness from FSE to the secondary phase was clear in 4 cases, drowsy in 13 cases, and uncertain due to continuous sedation in 2 cases.

The pathogens in cases of prodromal illness were *Streptococcus pneumoniae* meningitis in 1 case, *Haemophilus influenzae Type b* (Hib) meningitis in 1, Hib bacteremia in 1, rotavirus gastroenteritis in 1, influenza A infection in 2, chickenpox in 2, human herpesvirus-6 infection in 1, respiratory syncytial virus infection in 1, upper respiratory infection due to unknown viruses in 4, acute pneumonia due to unknown viruses in 1, unknown in 4.

Therapeutic hypothermia, which induced systemic cooling to 34 °C for 72 hours, was provided in 14 cases after secondary seizures. For 5 of these cases, steroid pulse therapy (methyl prednisolone 30 mg/ kg/ day for 3 days) and immunoglobulin therapy (1 g/ kg for single day) were simultaneously provided. For 2 of these cases, steroid pulse therapy was simultaneously provided. For 2 cases, steroid pulse therapy and immunoglobulin therapy were provided. For 2 cases, specific therapies were not given.

The neurologic sequelae were evaluated by PCPC score in 16 cases without underlying diseases that would affect the score. Seven cases were categorized as PCPC = 1, 3 cases were PCPC = 2, 5 cases were PCPC = 3, 1 case was PCPC = 4. In short, 56% of cases had neurologic sequelae. Incidentally, the non-AESD group had no neurologic sequelae.

5.3. Comparison between AESD group and non-AESD group in clinical courses **(Table 2）**

The age at onset was lower and the seizure duration was longer in the AESD group, but the differences were not statistically significant. The time until waking after FSE was significantly longer in the AESD group. The number of antiepileptic drugs to stop seizures was not significantly different among the two groups.

5.4. Comparison between AESD group and non-AESD group in laboratory data **（Table 3）**

The data were collected when we secured an intravenous catheter to administer the antiepileptic drugs. In the univariate analysis, the pH level was significantly lower and the $PvCO_2$ level was higher in the AESD group. Level of blood glucose, AST, ALT, LD, Cr, and NH_3 were also significantly higher in the AESD group. Other variables showed no significant

difference between the two groups. There were no cases with underlying diseases such as kidney disease, liver disease, metabolic disease, or respiratory disease affecting these values.

5.5.Cranial CT findings

Cranial CT was performed on all 19 cases in the AESD group, and 188 cases in the non-AESD group. There were no abnormal changes found in either group at the early phase.

5.6. Multivariate analysis

We excluded $PvCO_2$ from the predictors because pH and $PvCO_2$ were strongly correlated with each other, and pH had a lower P value than $PvCO_2$. We also excluded AST and LD but kept ALT as a predictor because they were strongly correlated with each other and AST and LD might be affected by hemolysis. Covariates for the multivariate logistic-regression analysis included time until waking after FSE, and levels of pH, blood glucose, ALT, Cr, and NH_3. The multivariate analysis identified the time until waking after FSE, and levels of ALT, blood glucose, and NH_3 as significant independent predictors for AESD.

5.7. Predicting scoring model for AESD

Cutoff points using the area under the receiver-operating-characteristics (ROC) curve for each variable were as follows: time until waking after FSE ≥ 11 hours, pH < 7. 014, ALT ≥ 28IU/l, Cr ≥ 0. 3mg/dl, blood glucose ≥ 228mg/dl, NH_3 ≥ 125μg/dl. Based on the estimates and their standard errors, we assigned 1 point for Cr ≥ 0. 3mg because it had the smallest effect among all predictors according to this analysis. We then assigned points to each predictor by comparing the ratio of estimates to its standard error with the equivalent ratio of Cr. We assigned 1 point for pH < 7. 014, Cr ≥ 0. 3mg/dl and 2 points for time until waking after FSE ≥ 11 hours, ALT ≥ 28IU/l, blood glucose ≥ 228mg/dl, and NH_3 ≥ 125 μg/dl (Table 4). We then derived the scores for 191 cases (AESD: 15 cases) that had no missing values for any predictor. Assuming that the score ≥ 4points was high risk, sensitivity and specificity were 93 % (14 / 15) and 91 % (160 / 176) respectively, and the positive-predictive value was 47 % (14 / 30) (Fig. 3).

When we also applied the scores to 8 cases of other acute encephalopathy and encephalitis with no missing values, which were excluded in the initial step, the sensitivity was 62 % (5 / 8).

5.8. Correlation between scores and prognosis

There was a positive correlation (Fig. 4) between our scoring model and the PCPC score in cases with no underlying diseases affecting the score (n = 13, rS = 0. 57). For all encephalopathy and encephalitis cases, our scoring model was also positively correlated with PCPC score (n = 21, rS = 0. 64).

6. Discussion

The pathogenesis of AESD has been suggested to be related to excitotoxic injury because AESD does not show hypercytokinemia, the IL-6 levels in the cerebrospinal fluid are elevated to protect the brain against the ischemic and excitotoxic damage, and the Glx (glutamate/glutamine complex) on proton MR spectroscopy (MRS) is elevated as an excitatory neurotransmitter [6][7][8]. Many cases of AESD have been reported in Japan. Genetic predispositions have also been reported and some relevant gene mutations and polymorphisms have been found [9][10]. The strength of excitement seems to be affected by these factors.

In this study, the characteristics of cases developing AESD were 1) a longer time until waking after FSE, 2) higher degree of respiratory acidemia, and high levels of liver enzymes such as AST, ALT and LD, 3) a high Cr level, 4) hyperammonemia, and 5) hyperglycemia at the onset. These features might show that the excitement of seizures was stronger in the AESD group than in the non-AESD group.

It is possible that the time until waking was affected by antiepileptic drugs, but there was no significant difference in the number of drugs used in the two groups. The consciousness disorders of AESD might be long because of the strong seizure itself and the secondary respiratory and cerebral circulation failure. A previous study reported that cases with a consciousness disorder lasting 12 hours after FSE were at high risk of acute encephalopathy

[11]. The previous study also reported that some AESD patients and patients who took long time to wake after seizures were in a state of non-convulsive status epileptics (NCSE) [12][13][14].

The acidemia might be caused by circulation failure, increase of the lactic acids due to cramps of the skeletal muscles, and respiratory depression. However, seizure duration was not simply related to the strength of the excitotoxin because it was not significantly different between the AESD and non-AESD groups. The lactic acids levels might be theoretically higher in AESD, but no significant difference between groups could be found, largely because of many missing values.

High levels of AST, ALT, LD, NH_3, and Cr could indicate liver and kidney damage due to respiratory and circulation failure. Several reports have examined the positive correlation between AST and prognosis in acute encephalopathy [15][16].

Hyperglycemia would be caused by high levels of stress-related hormones such as catecholamine and cortisol. Several studies have reported that acidemia and hyperglycemia exacerbate the prognosis [15][17][18][19][20].

Cranial CT was not a useful predictor because it did not show remarkable changes at the early phase.

In this report, we could explore the clues of early diagnosis of AESD by a scoring model that we devised. The sensitivity and specificity of this scoring model were high, but the positive-predictive value would depend on the incidence of AESD. Compared with the incidence of AESD in the previous reports, the positive-predictive value was 31.7%–61.7 % [11][20][21][22].

Cases with high scores tended to have neurologic sequelae. In this report, many AESD cases experienced several levels of neurologic sequelae. Cases with high scores should be observed carefully by electroencephalogram to confirm whether they are in a state of NCSE.

AESD has been treated with steroid pulse therapy and immunoglobulin therapy; however, these treatments would not be effective for AESD because hypercytokinemia is not the pathogenic mechanism as in other subtypes of acute encephalopathy [20]. On the other hand, early therapeutic hypothermia would be effective in preventing secondary energy failure after brain damage [23].

Imataka reported that early introduction of therapeutic hypothermia immediately after FSE reduced the number of cases developing AESD [24]. Nakagawa et al. also reported that maintaining normothermia immediately after FSE reduced the prevalence of neurologic sequelae [25]. However, in childhood acute encephalopathy hypothermia is not effective if 12 hour or more has passed after the brain damage [26]. Several studies have reported that an axonal damage marker, tau protein in cerebrospinal fluid and Glx on MRS, were already elevated on day 2–3 [7][27]. But, because of the high invasiveness of therapy, it has been difficult to introduce it without obvious evidence of encephalopathy. AESD has been treated after secondary seizures and under pathognomonic MRI findings. However, at that point it may be too late to ameliorate brain damage. Therefore, early intervention is worth considering for cases with high risks, as identified by our scoring model.

Our scoring model would also be useful in the early diagnosis of acute encephalopathy and encephalitis other than AESD with FSE. The pathogenesis of acute encephalopathy other than AESD would be hypercytokinemia, and damage to the brain and other organs would appear strongly in the early phase, as in the case of our study subjects.

7. Limitations of this study

First, because this study was conducted at a single institution, the number of AESD cases was limited. There is a possibility that the sensitivity, specificity and cut-off point of our scoring model would change with an increase in the sample size. Second, we investigated FSE patients

only. However, some AESD cases do not start with FSE. Third, we did not consider NCSE because we included only visible seizures to calculate seizure duration. Fourth, we did not unify the interventional method. It is possible that the prognosis or incidence of AESD was affected by the interventions.

We need to investigate cases in other institutions, increase the case number and verify the reproducibility of this study. Because there were significant differences between AESD and non-AESD cases in clinical course and laboratory data, we could establish an accurate scoring model with further analysis.

8. Conclusions

Our scoring model would enable early diagnosis of AESD. Cases with high scores should be observed carefully and early intervention should be considered.

Conflict of interest

All authors have no conflicts of interest to disclose.

References

[1]Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 2012;34:337-43.

[2]Kimura S, Ohtuki N, Nezu A, Tanaka M, Takeshita S. Clinical and radiological variability of influenza-related encephalopathy or encephalitis. Acta Paediatr Jpn 1998;40:264-70.

[3]Yoshikawa H, Yamazaki S, Watanabe T, Abe T. Study of influenza-associated encephalitis/encephalopathy in children during the 1997 to 2001 influenza seasons. J Child Neurol 2001;16:885-90.

[4]Bekci T, Aslan K, Bilgici MC, Onaral CS, Yosmaet E. A missed diagnosis: Acute encephalopathy with biphasic seizures and late reduced diffusion. Clin Neurol Neurosurg 2014;127:161-2.

[5]Fiser DH. Assessing the outcome of pediatric intensive care. J Pediatr 1992;121:68-74.

[6]Ichiyama T, Suenaga N, Kajimoto M, Tohyama J, Isumi H, Kubota M, et al. Serum and CSF levels of cytokines in acute encephalopathy following prolonged febrile seizures. Brain Dev 2008;30:47-52.

[7]Takanashi J, Oba H, Barkovich AJ, Tada H, Tada H, Tanabe Y, Yamanouchi H, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304-9.

[8]Takanashi J, Tada H, Terada H, Barkovich AJ. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. AJNR Am J Neuroradiol 2009;30:132-5.

[9]Saitoh M, Shinohara M, Hoshino H, Kubota M, Amemiya K, Takanashi JL,et al. Mutations of the SCN1A gene in acute encephalopathy. Epilepsia 2012;53:558-64.

[10]Shinohara M, Saitoh M, Takanashi J, Yamanouchi H, Kubota M, Goto T, et al. Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. Brain Dev 2011;33:512-7.

[11]Nagase H,Nakagawa T,Aoki K,Fujita K,Saji Y,Maruyama A,et al. Therapeutic indication for acute encephalopathy using predictors in patients with complex febrile seizures(in Japanese). J Jpn Pediatr Soc 2010;114:858-64.

[12]Okumura A. Kyuseinosyo ni okeru noha (in Japanese). No to Hattatsu (Tokyo) 2011;43:110-6.

[13]Carrera E, Claassen J, Oddo M, Emerson RG, Mayer SA, Hirsch LJ. Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. Arch Neurol 2008;65:1612-8.

[14]Komatsu M, Okumura A, Matsui A, Kitamura T, Sato T, Shimizu T et al. Clustered subclinical seizures in a patient with acute encephalopathy with biphasic seizures and late reduced diffusion. Brain Dev 2010; 6: 472–6.

[15]Nagao T, Morishima T, Kimura H, et al. Prognostic factors in influenza-associated encephalopathy. Pediatr Infect Dis J 2008;27:384–9.

[16]Maegaki Y, Kondo A, Okamoto R, Inoue T, Konishi K, Hayashi A, et al. Clinical characteristics of acute encephalopathy of obscure origin: a biphasic clinical course is a common feature. Neuropediatrics. 2006;37:269-77.

[17]Rathakrishnan R, Sidik NP, Huak CY, Wilder-Smith EP. Generalised convulsive status epilepticus in Singapore: clinical outcomes and potential prognostic markers. Seizure 2009;18:202–5.

[18]Cronberg T, Rytter A, Asztély F, Söder A, Wieloch T. Glucose but not lactate in combination with acidosis aggravates ischemic neuronal death in vitro. Stroke 2004;35:753-7.

[19]Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, Kothare SV, et al. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. PLoS One 2012;7:e47474.

[20] Hayashi N, Okumura A, Kubota T, Tsuji T, Kidokoro H, Fukasawa T, et al. Prognostic factors in acute encephalopathy with reduced subcortical diffusion. Brain Dev 2012;34:632-9.

[21]Shiohama T, Kanazawa M, Anzai S, Kato I, Abe K, Takeda N, et al. Clinical study of status epilepticus in children (in Japanese). J Jpn Pediatr Soc 2010;114:956-60.

[22]Maegaki Y, Kurozawa Y, Hayashi A, Tsuji Y, Okamoto R, Kondo A,et al. An early diagnosis of acute encephalopathy using early clinical, laboratory, and neuroimaging findings(in Japanese). J Jpn Pediatr Soc 2006;110:1550-7.

[23]Iwata O, Iwata S, Thornton JS, De Vita E, Bainbridge A, Herbert L, et al. "Therapeutic time window" duration decreases with increasing severity of cerebral hypoxia-ischaemia under normothermia and delayed hypothermia in newborn piglets. Brain Res 2007;18:173-80.

[24]Imataka G. Japanese Journal of Pediatrics 2012 (in Japanese). Tokyo:Nihon-syouni-ijisyuppansya 2012.

[25]Nakagawa T, Fujita K, Saji Y, Maruyama A, Nagase H, et al. Induced hypothermia/ normothermia with general anesthesia prevents neurological damage in febrile refractory status epilepticus in children (in Japanese). No To Hattatsu (Tokyo) 2011;43:459-63.

[26]Kawano G, Iwata O, Iwata S, Kawano K, Obu K, Kuki I, et al. Determinants of outcomes following acute child encephalopathy and encephalitis: pivotal effect of early and delayed cooling. Arch Dis Child 2011;96:936-41.

[27]Tanuma N, Miyata R, Kumada S, Kubota M, Takanashi J, Okumura A, et al. The axonal damage marker tau protein in the cerebrospinal fluid is increased in patients with acute encephalopathy with biphasic seizures and late reduced diffusion. Brain Dev 2010; 32:435–9.

Figure legends

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

Fig. 2. We categorized the 223 cases of FSE into the AESD group and the non-AESD group and excluded 10 cases from analysis because of other acute encephalopathy or encephalitis.

Fig. 3. Receiver-operator characteristic curve for the scoring model. For a cutoff of 4points, sensitivity and specificity were 93% and 91%, respectively. The area under the ROC curve of this scoring model was 0.96.

Fig. 4. Correlation between score and prognosis. The score had positive correlation with PCPC score on AESD and all encephalopathy and encephalitis.

Tables and legends

Table 1

Pediatric Cerebral Performance Category Scale.

Clinical features	Category	Score
▪ normal for age ▪ school-age child attending regular school classroom	normal	1
▪ conscious, alert and able to interact at an age-appropriate level ▪ school-age child attending regular school classroom but grade perhaps not appropriate for age ▪ may have a mild neurologic deficit	mild disability	2
▪ conscious ▪ sufficient cerebral function for age-appropriate independent activities of daily life ▪ school-age child attending special education classroom ▪ may have learning deficit	moderate disability	3
▪ conscious ▪ dependent on others for daily support because of impaired brain function	severe disability	4
▪ any degree of coma without any of the criteria for brain death ▪ unawareness even if awake in appearance without interaction with the environment ▪ cerebral unresponsiveness ▪ no evidence of cortical function and not aroused by verbal stimuli ▪ possibly some reflexive responses, spontaneous eye opening and/or sleep-wake cycles	coma or vegetative state	5
▪ apnea OR ▪ areflexia OR ▪ electroencephalographic (EEG) silence	brain death	6

Table 2

Comparison between AESD and non-AESD in the clinical course.

	AESD (n=19)		non-AESD (n=194)		*P* value
clinical course	**median**	**range**	**Median**	**range**	
age at onset (months)	19	(7–49)	23	(2–168)	0.17
seizure duration (minutes)	50	(30–90)	40	(30–100)	0.06
time until waking (hours)	11.0	(7.0–37.0)	4. 0	(0.5–17.0)	<0.01
number of drugs used	2	(1–3)	1	(0–3)	0.55

Table 3

Comparison of laboratory data in AESD and non-AESD cases.

	AESD			non-AESD			*P* value
laboratory data	**median**	**range**	**n**	**median**	**range**	**n**	
pH	7.014	(6.746–7.209)	17	7. 262	(6.778–7.561)	187	<0.01
$PvCO_2$	88.8	(28.0–226.0)	17	48. 5	(20.4–182.8)	187	<0.01
lactic acids (mg/dl)	38	(19–66)	9	22	(6–83)	102	0.87
sodium (mEq/l)	137.3	(125.3–147.9)	19	136. 0	(124.5–167.0)	194	0.14
AST (IU/l)	49	(24–118)	19	36	(13–112)	194	<0.01
ALT (IU/l)	25	(7–82)	19	15	(5–57)	194	<0.01
LD (IU/l)	329	(245–410)	19	310	(119–714)	194	0. 02
Cr (mg/dl)	0. 34	(0. 26–1. 07)	19	0. 27	(0. 07–1. 47)	194	<0. 01
platelet count (10^4/μl)	30. 4	(15. 6–45. 0)	18	27. 1	(4. 3–60. 2)	194	0. 16
blood glucose (mg/dl)	244. 5	(14–392)	18	159	(13–381)	193	<0. 01
ammonia (μg/dl)	126. 5	(23. 0–307. 0)	18	72. 0	(14. 0–286. 0)	190	<0. 01

Table 4

Multiple predictors of AESD in our scoring model.

risk factor	Estimate: a	SE: b	a/b (ratio between Cr)	*P* value	Score points
pH<7. 014	-0. 975	0. 269	-3. 622 (1. 389)	<0. 01	1
ALT (IU/l) ≥28	-1. 264	0. 271	-4. 666 (1. 789)	<0. 01	2
blood glucose (mg/dl) ≥228	-1. 430	0. 284	-5. . 034 (1. 930)	<0. 01	2
time until waking (hours) ≥11. 0	-2. 084	0. 353	-5. 905 (2. 264)	<0. 01	2
Cr (mg/dl) ≥0. 3	-0. 672	0. 258	-2. 608 (1)	<0. 01	1
ammonia (μg/dl) ≥125	-1. 425	0. 230	-4. 756 (1. 824)	<0. 01	2

Fig. 1

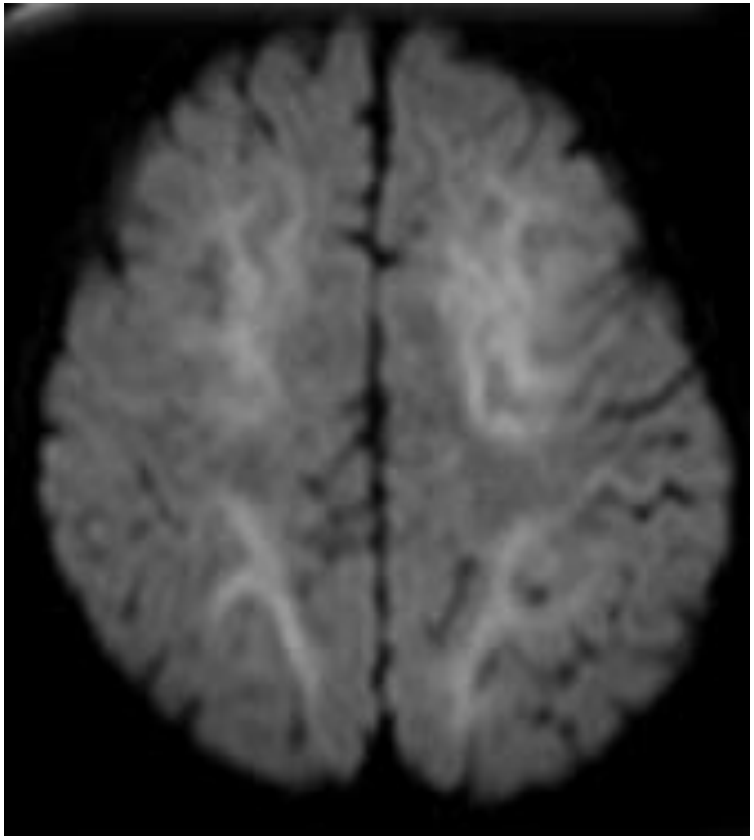


Fig. 2

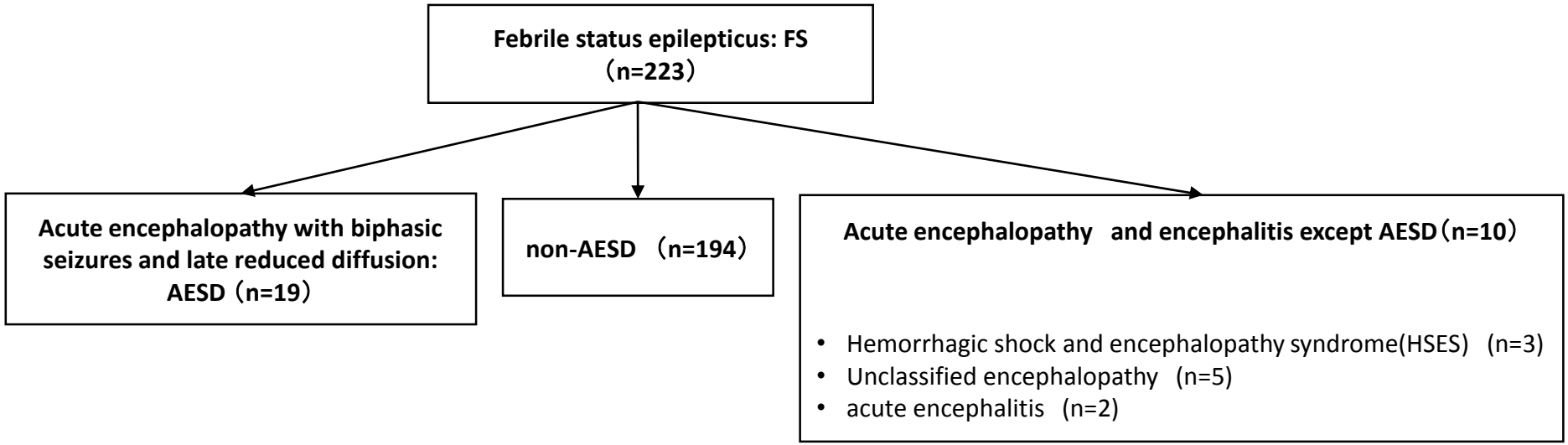
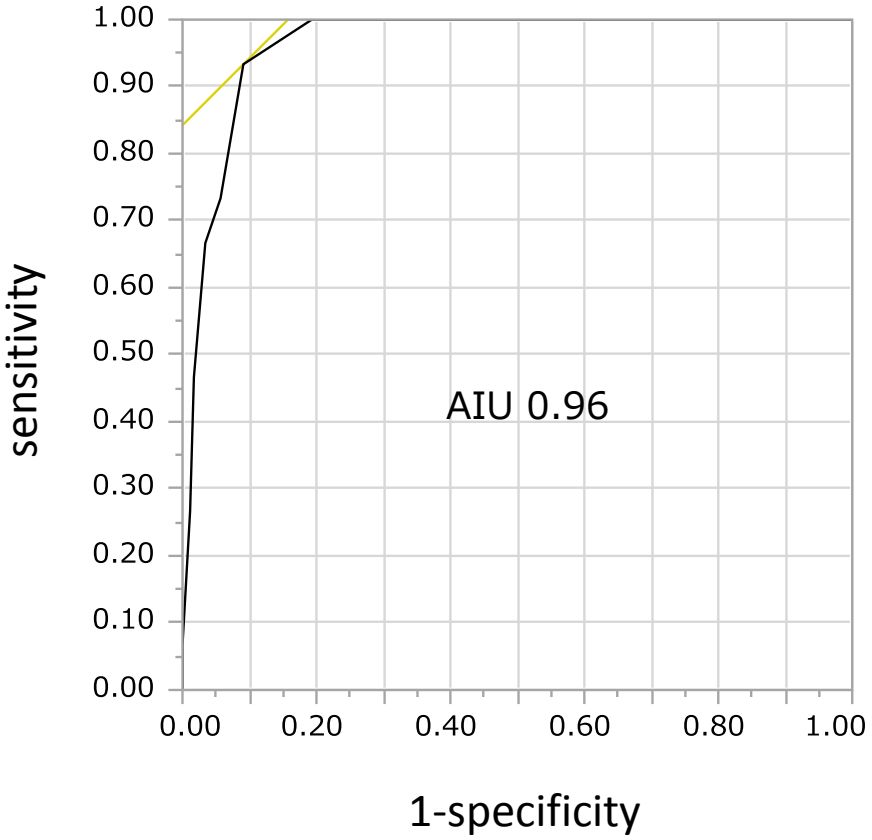

Febrile status epilepticus: FS
（n=223）
Acute encephalopathy with biphasic seizures and late reduced diffusion: AESD（n=19）
non-AESD （n=194）
Acute encephalopathy and encephalitis except AESD（n=10）
• Hemorrhagic shock and encephalopathy syndrome(HSES) (n=3)
• Unclassified encephalopathy (n=5)
• acute encephalitis (n=2)

Fig. 3


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
sensitivity
AIU 0.96
0.00
0.20
0.40
0.60
0.80
1.00
1-specificity