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Original article

Detailed clinical course of fatal acute encephalopathy in children

Kazumi Tomioka [a,*], Masahiro Nishiyama [a], Hiroaki Nagase [a], Yusuke Ishida [a], Tsukasa Tanaka [a], Shoichi Tokumoto [b], Hiroshi Yamaguchi [b], Daisaku Toyoshima [b], Azusa Maruyama [b], Kyoko Fujita [c], Kazunori Aoki [d], Yusuke Seino [d], Kandai Nozu [a], Noriyuki Nishimura [a], Hiroshi Kurosawa [d], Kazumoto Iijima [a]

[a] *Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan*
[b] *Department of Neurology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan*
[c] *Department of Emergency and General Medicine, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan*
[d] *Department of Pediatric Critical Care Medicine, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan*

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Abstract

Objective: Although the mortality among previously healthy children with acute encephalopathy (AE) is approximately 5%, their detailed clinical course has not been clarified. The objective of the present study was to describe the detailed clinical course, in minutes, of fatal AE.

Methods: We retrospectively reviewed the medical records of five patients (from 6 months to 14 years of age) who previously had no neurological disorders and were diagnosed with brain death due to AE between 2002 and 2018 at Kobe Children's Hospital.

Results: The initial clinical symptoms were convulsion in three cases and impaired consciousness in two. The earliest noted brain imaging abnormality was 7.5 h after neurological symptom detection. Liver enzymes and creatinine levels increased at initial examination, and sodium elevated gradually. All patients met the criteria of systemic inflammatory response syndrome, disseminated intravascular coagulation, and shock within 14 h of symptom detection. High dose steroids and targeted temperature management were initiated 3.5–14 h after onset. Despite these therapies, patients were diagnosed with brain death from 16 h to 4 days after initial neurological symptoms. AE diagnoses were made between 4 h 29 min and 4 days after initial neurological symptoms and included hemorrhagic shock and encephalopathy syndromes, Reye-like syndrome, and acute necrotizing encephalopathy in two, two, and one patient(s), respectively.

Conclusions: We revealed the time series' of clinical events (e.g. SIRS, shock, DIC, AE diagnosis, brain death, and treatments) and laboratory findings relative to initial neurological symptom in fatal AE.

Keywords: Acute encephalopathy; Brain death; Pediatrics

1. Introduction

Acute encephalopathy (AE) is a generic term for acute brain dysfunction, caused by a viral infection in many cases [1]. Its main symptoms are acute onset impaired consciousness and signs of increased intracranial pressure, often accompanied by convulsions or

* Corresponding author at: Department of Pediatrics, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-Cho, Chuo-Ku, Kobe, Hyogo 650-0017, Japan.
E-mail address: toimoka@med.kobe-u.ac.jp (K. Tomioka).

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seizures [1,2]. The mortality associated with AE is 5.6% and many survivors have motor and intellectual disabilities or epilepsy [1,2]. Severe cases of the disease run a fulminant course, with rapid development of coma and signs of systemic inflammatory response syndrome (SIRS), shock, multiple organ failure (MOF), and disseminated intravascular coagulation (DIC) [1,2]. A nationwide survey of pediatric AE revealed that 11 patients died with hemorrhagic shock and encephalopathy syndrome (HSES), and 11 patients died with acute necrotizing encephalopathy (ANE) between 2007 and 2010 [2]. Detailed neuroimaging of 22 patients, including 8 fatal cases, was presented in the largest case series for HSES yet published [3]. The outcomes for and treatment of 34 patients, including 10 fatal cases, were reported in the largest case series of ANE to date [4]. However, these studies did not focus on minute-by-minute clinical time courses [2–4]. In a previous retrospective study, we analyzed clinical and laboratory risk factors for mortality among children with seizure and/or impaired consciousness accompanied by fever, and reported that aspartate aminotransferase (AST) was associated with mortality [5]. However, the time courses of fatal AE in this patient group were unknown. Given this background, the purpose of the present study was to describe the clinical course of fatal acute encephalopathy with a temporal resolution of minutes. Specifically, we focus on the time series' of clinical events (e.g. SIRS, shock, DIC, brain death, and treatments) and laboratory findings relative to initial neurological symptom.

2. Subjects and methods

2.1. Patients

Kobe Children's Hospital (KCH) provides tertiary pediatric services to the Hyogo prefecture (population: 5.6 million), and approximately 100 children are admitted to KCH's pediatric intensive care unit (PICU) annually owing to neurological symptoms with fever. We used our database consisted of consecutive patients who were admitted to KCH with impaired consciousness and/or seizure with fever. Patients' diagnoses in our database included, for example, complex febrile seizures (FS) or AE. We extracted the patients who previously had no history of neurologic disease (Pediatric Cerebral Performance Category [6], PCPC = 1) and were ultimately diagnosed with brain death (PCPC = 6) because of AE from our database between October 2002 and March 2018, and reviewed their medical records.

2.2. Variables

We retrospectively reviewed the patients' clinical courses, including the timing of their initial presentation, clinical criteria, examination, and treatment. Clinical criteria included SIRS, DIC, shock, and a diagnosis of AE. Examinations included laboratory assessments conducted 24 h after symptom onset, microbiological cultures of blood and cerebrospinal fluid (CSF), rapid assays for influenza virus (Flu), RS virus (RSV), rotavirus and real-time polymerase chain reaction for human herpes virus types 6 and 7 (HHV-6 and -7), computed tomography (CT) imaging, magnetic resonance imaging (MRI), and electroencephalography (EEG). EEGs taken in patients with acute encephalopathy feature diffuse high amplitude slow waves or rhythmic waves [7]. Thus, we recorded diffuse slow waves and electrical seizure activity, as was proposed by Young, et al [8]. Patients were treated via intubation, administration of anti-epileptic drugs, inotropic agents and/or high dose steroids (HDS; methylprednisolone 30 mg/kg), targeted temperature management (TTM; 36.0 ± 0.5 °C for at least 48 h using a cooling blanket), barbiturate coma therapy (BCT; bolus injections of 1–2 mg/kg of thiamylal until we confirmed the burst-suppression pattern on EEG, maintenance dosage 1–5 mg/kg/h), and continuous hemodiafiltration (CHDF).

2.3. Clinical definitions

We defined onset time as that when initial neurological symptoms, including convulsions or impaired consciousness, were first recognized in accordance with criteria determined in previous studies [5,9,10]. We also defined brain death as including the following three factors: coma with EEG amplitude <10 μV, lack of brainstem reflexes, and apnea. The criteria outlined in the International Consensus Conference on Pediatric Sepsis and Organ Dysfunction were used to determine SIRS and shock [11]. Briefly, shock is defined as sustained hypotension after sufficient adequate infusion (≤-2SD below normal blood pressure determined based on patient age). The criteria outlined by the Japanese Association for Acute Medicine were also used for the determination of DIC [12]. We used two criteria for the diagnosis of AE: impaired consciousness for more than 24 h, or abnormal brain imaging [13]. HSES, Reye-like syndrome, and ANE were diagnosed in accordance with previous reports [14–16].

2.4. Ethical approval

The present study was approved by the local ethical committee of Kobe University Graduate School of Medicine and KCH, which waived the need for informed consent given that this was a retrospective observational study.

3. Results

3.1. Patients characteristics (Table 1)

The medical records of two boys and three girls, ranging in age from 6 months to 14 years, were examined in the present study. Symptoms prior to onset included fever, cough, diarrhea, and vomiting for one or two days in four of the five cases. The median patient body temperature on admission was 39.6 °C (38.1–41.0 °C). Initial neurological symptoms included convulsions in three patients and impaired consciousness in two. The duration of convulsion at onset was from 3 to 15 min (unknown in case 5). Seizures were controlled with diazepam, and/or midazolam in case 3, 4, and 5. Phenobarbital and thiamylal were administered to terminate clinical and electrical seizures in case 1 and 2. Cases 3, 4 and 5 tested positive for Flu A and B, respectively. All other virus examinations were negative. Blood and CSF cultures for bacteria were also negative in all patients. Abnormalities on brain imaging included edema, bleeding, and necrosis. Final diagnoses included HSES, Reye-like syndrome, and ANE in two, two, and one patient(s), respectively.

3.2. Time course of clinical events relative to onset (Table 2, Fig. 1)

Four patients (cases 1–4) were hospitalized 1 h after initial neurological symptom onset, and one patient (case 5) was hospitalized 11 h after onset. Two patients (cases 1 and 4) were admitted directly to our hospital. Patients 2 and 5 were transferred 13 h after initial symptom onset, while patient 3 was transferred after only 4 h. Initial head CTs performed within approximately 3 h of symptom onset revealed no abnormalities in three patients (cases 1, 3, and 4). In case 2, an initial head CT was performed 12 h after symptom onset and showed that brain stem edema was already evident. In case 5, the initial CT performed on autopsy at 16 h identified brain edema but no other cause of death, such as bleeding or a space-occupying lesion. All the cases described here fulfilled the SIRS criteria immediately upon hospitalization (1–12 h after symptom onset). They presented with DIC and shock almost simultaneously (4–14 h after onset). Intubation was performed in all cases 4–14 h after symptom onset, and inotropic agents were started in all cases 6–15 h after onset. Initial HDS was administered in 4 cases (cases 1–4) at 3 h 35 min–13 h 40 min after onset. TTM and BCT or continuous midazolam infusion were performed in two cases (case 1 and 2) at 8 h and 13 h 40 min, respectively. Brain imaging revealed abnormalities such as brain edema at 7 h 30 min-4 days after onset, and they were diagnosed with AE between 4 h 29 min and 4 days after initial neurological symptoms. Continuous EEG was

Table 1
Patients characteristics, symptoms, and diagnoses.

Case	Sex	Age	Symptoms prior to AE onset	Body temperature in admission	Initial neurological symptom (duration of convulsion)	Use of anti epileptic drugs	Etiology	Abnormalities of brain imaging	Diagnosis
1	Female	0 y6 m	None	38.1 °C	Convulsions (15 min)	DZP iv, MDL iv, MDL ci, PB iv, THI ci	Not detected	Edema	Reye-like syndrome
2	Male	1 y1 m	Fever (−1 day) Vomiting (-1 day)	39.6 °C	Convulsions (3 min)	PB sup, DZP iv, MDL ci	Not detected	Edema, diffuse atrophy	Reye-like syndrome
3	Female	8 y	Fever (−1 day)	39.5 °C	Impaired consciousness	MDL iv	Flu A	Bleeding, brain stem necrosis, edema, hernia	HSES
4	Female	8 y	Fever (−1 day) vomiting, diarrhea (−1 day)	39.8 °C	Impaired consciousness	DZP iv, MDL iv	Flu A	Symmetrically distributed brain lesions of the thalamus, brain stem necrosis	ANE
5	Male	14 y	Fever, cough (−2 days) vomiting, diarrhea (−1 day)	41.0 °C	Convulsions (unknown)	DZP iv	Flu B	Edema	HSES

AE, acute encephalopathy; ANE, acute necrotizing encephalopathy; DZP, diazepam; Flu; influenza; HSES, hemorrhagic shock and encephalopathy syndrome; MDL, midazolam; PB, phenobarbital; THI, thiamiral; iv, intravenous infusion; ci, continuous infusion; sup, suppository.

Table 2
Clinical course of events relative to symptom onset time for each case.

Case	Hospitalization (our hospital)	Initial head CT (abnormality)	SIRS	DIC	Shock	intubation	Start of inotropic agents	HDS	TTM& BCT	Diagnosis of AE syndrome	Brain death
1	0 h28 m	1 h22 m (none)	1 h21 m	n.p.	n.p.	4 h43 m	9 h40 m	7 h40 m	8 h0 m	day4	day4
2	0 h (13 h30 m)	12 h00 m (brain edema)	9 h00 m	13 h40 m	13 h40 m	13 h40 m	13 h40 m	13 h40 m	13 h40 m	12 h00 m	36 h
3	1 h (4 h20 m)	1 h0 m (none)	4 h20 m	4 h29 m	5 h30 m	5 h00 m	6 h14 m	3 h35 m	n.d.	4 h29 m	40 h
4	1 h0 m	1 h00 m (none)	1 h0 m	4 h35 m	8 h0 m	7 h20 m	9 h30 m	9 h40 m	n.d.	7 h30 m	48 h
5	11 h (13 h)	after death (brain edema)	11 h36 m	11 h36 m	13 h10 m	13 h36 m	14 h49 m	n.d.	n.d.	16 h	16 h26 m

Display shows the duration from symptom onset. h, hour(s); m, minute(s); AE, acute encephalopathy; BCT, barbiturate coma therapy; CT, computed tomography; DIC, disseminated intravascular coagulation; HDS, high dose steroids; SIRS, systemic inflammatory response syndrome; TTM, targeted temperature management; n.p., not presented; n.d., not done.

performed 24 h after symptom onset in three cases, and electrical seizures were detected in two (cases 1 and 3). Some patients also showed diffuse slow wave patterns when seizures were not occurring (cases 1, 3, and 4), with gradually decreasing amplitudes. Low amplitude (<10 μV) waves were observed 14 h after symptom onset in the earliest case (case 4). Despite intensive treatment, all patients were ultimately diagnosed with brain death between 16 h and 4 days after initial symptom onset.

3.3. Laboratory data 24 h after symptom onset (Table 3, Fig. 2)

White blood cell counts (WBC) were often elevated, but there were no consistent pattern of change over time. Platelet counts were normal or slightly elevated at initial examination, but tended to decrease afterward. Prothrombin times/international normalized ratios (PT/INRs) were often elevated after 4 h from symptom onset. Initial AST levels were also slightly elevated within 3 h of symptom onset in cases 1 and 4; AST levels as well as other liver enzymes increased dynamically in all patients 4 h after symptom onset (Fig. 2a). Initial creatinine levels were elevated (greater than the 97.5 percentile of standard values for each patients' respective age) in all patients (0.60–2.72 mg/dL, Fig. 2b) [17]. Initial sodium levels were greater than 141 mmol/L. Sodium levels were almost within the normal range at initial examination, but increased gradually within 24 h of symptom onset in all patients (Fig. 2c). Both hyperammonemia and hypoglycemia were detected in one patient (case 2). All patients had severe metabolic acidosis with abnormally low base excess (BE) at initial examination that continued below normal within 24 h, although it improved over time in two cases (cases 3 and 4).

4. Discussion

The final diagnoses determined in the cases presented here include Reye-like syndrome, HSES, and ANE. These are AE subtypes associated with a high mortality rate [1]. While the cases described here were all terminal, detailed descriptions of their treatments and clinical courses remain important as these have not previously been reported on a minute-by-minute timescale for cases of fatal AE. Further, to the best of our knowledge, this manuscript is the first to document the evolution of AE at this timescale. Below we focus our discussion on aspects of the cases pertinent to the timing of interventions.

4.1. The timing of clinical events relative to onset

The earliest diagnosis of AE was rendered at 4 h 29 min after symptom onset (case 3). In contrast, the

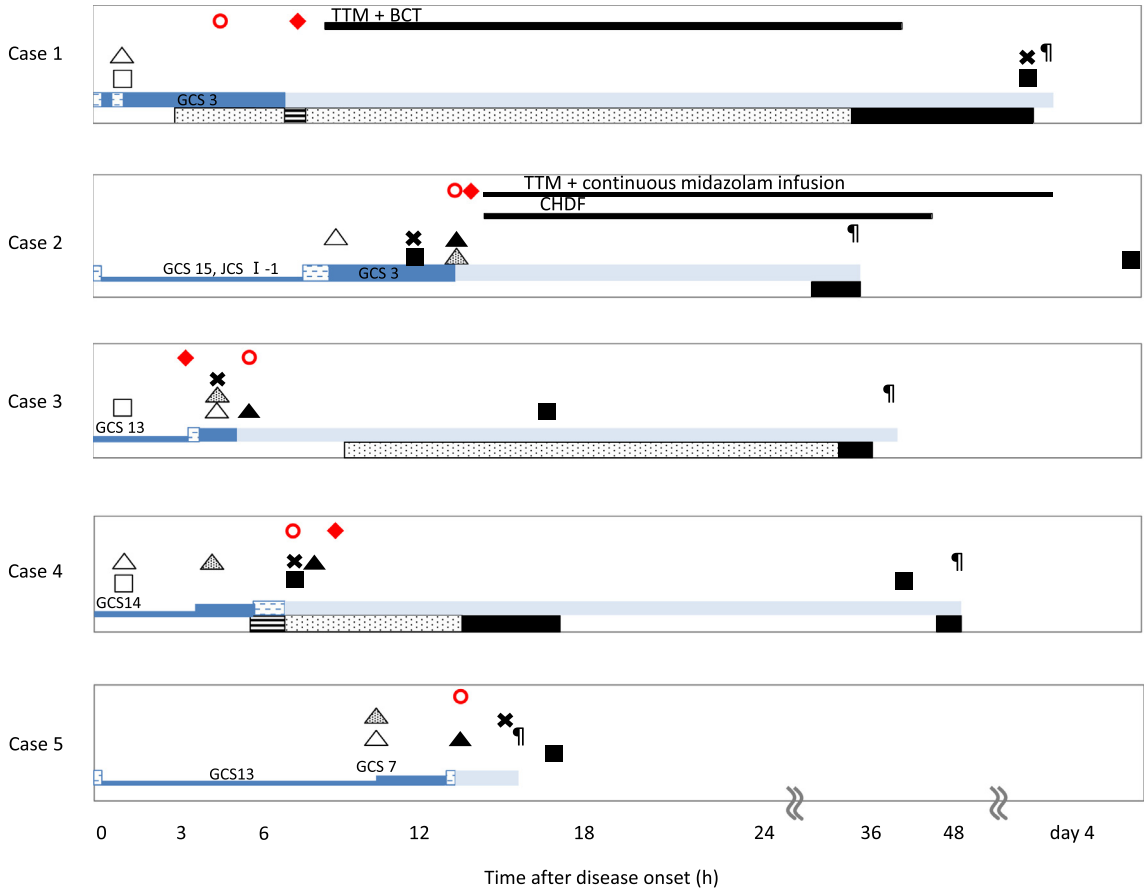

Fig. 1. Clinical time courses for all patients. Case 1: She was hospitalized with clinical seizure. Initial CT was normal. She was intubated at 4 h 43 min because of unconsciousness and clinical seizure. High dose steroids (HDS) were administered at 7 h 40 min. Continuous electroencephalogram (cEEG) from 3 h after onset identified slow wave and electrical seizures. Barbiturate coma therapy (BCT; bolus dosage 39.2 mg/kg, maintenance dosage 5 mg/kg/h) with targeted temperature management (TTM) was initiated 9 h after symptom onset because of unconsciousness and refractory electrical seizures. On day 4, diffuse brain edema was identified, and she was diagnosed with Reye-like syndrome and consequently died. Case 2: He was hospitalized with clinical seizure and impaired consciousness, and intubated at 13 h 40 min because this deteriorated to unconsciousness with recurrent clinical seizure. Brain edema was identified on initial CT, and he was diagnosed with Reye-like syndrome at 12 h. Intensive therapies including HDS, TTM, and continuous hemodiafiltration (CHDF) were initiated. However, low voltage (<10 μV) was identified on EEG, and he died at 36 h after onset. Case 3: She was hospitalized with impaired consciousness. Initial CT was normal. HDS was administered at 3 h 35 min because influenza encephalopathy was suspected. She was diagnosed with hemorrhagic shock and encephalopathy syndrome (HSES) because of multiple organ failure (MOF) and disseminated intravascular coagulation (DIC) at 4 h 29 min. Intensive therapies including intubation and inotropic agents were initiated but her condition deteriorated rapidly and she died at 40 h after onset. Case 4: She was hospitalized with impaired consciousness. Initial CT was normal. Consciousness level deteriorated with recurrent seizures. Second CT revealed symmetrically distributed brain lesions of the thalamus, and she was diagnosed with acute necrotizing encephalopathy (ANE) at 7 h 30 min. Intensive therapy including intubation and HDS was conducted but she developed shock and died at 48 h. Case 5: He was hospitalized with clinical seizure and impaired consciousness. Consciousness level deteriorated, and clinical seizure recurred at approximately 12 h. MOF and DIC were identified. He developed shock, and was diagnosed with HSES at 16 h. Despite intensive therapies, he died at 16 h 26 m. CT at autopsy identified brain edema.

longest duration between initial symptom onset and the diagnosis of AE in the cases herein described was 4 days (case 1). Our finding that these patients presented with SIRS, DIC, or shock criteria was consistent with previous reports of fatal AE [1,2], although these previous studies did not report the time lags between presenting with these criteria, and AE diagnoses or onset of neurological symptoms. We observed that SIRS criteria were met earliest, followed by DIC, and shock. All patients met the SIRS criteria at a relatively early stage in their disease progression or immediately upon admission, though we did not commence intensive therapies at that time because we were unable to predict fulminant courses. Criteria for SIRS, DIC, and shock were also met prior to the diagnoses of AE presented here.

Head CTs performed approximately 3 h after symptom onset were normal in three patients. The earliest noted brain imaging abnormality was 7.5 h after symptom onset. Among 10 patients with HSES, 8% of initial head CTs were normal [3]; thus the normal brain imaging findings that we report a few hours after symptom onset ultimately did not preclude the evolution of an AE diagnosis thereafter.

Table 3
Laboratory data collected within 24 h of symptom onset.

Case	Duration from onset	WBC	Plt	PT/INR	AST	ALT	LDH	Cre	Na	Glu	NH_3	pH	BE
1	1 h22 m	27900	42.3	0.99	63	22	463	0.60	142	283	127	7.061	−16.5
	6 h29 m	18800	22.8	n.t.	504	54	2199	0.40	145	88	41	7.366	−4.6
	12 h23 m	7100	12.8	2.31	677	87	3419	0.33	145	127	n.t.	7.468	−4.0
	22 h01 m	5000	16.6	1.67	489	115	2852	0.34	150	144	n.t.	7.335	−4.0
2	9 h00 m	44690	71.1	n.t.	7230	3410	7650	0.8	148	10	874	n.t.	n.t.
	13 h40 m	43200	51.7	4.57	6122	2972	6680	1.02	146	88	>1000	7.026	−21.5
	18 h30 m	20000	24.1	6.53	3720	1610	3860	0.87	149	319	376	7.117	−19.0
	23 h00 m	21400	23.7	n.t.	3710	1650	3740	0.62	155	296	180	7.271	−8.8
3	4 h28 m	11200	15.1	2.29	1760	1058	3610	1.51	142	23	25	7.175	−9.6
	7 h46 m	13200	11.0	4.08	896	484	2680	1.29	142	162	n.t.	n.t.	n.t.
	9 h59 m	12100	9.7	4.17	1671	471	3279	1.24	142	166	276	7.395	−2.0
	19 h21 m	6800	10.7	3.2	9720	4581	10060	2.46	157	147	120	7.234	−5.1
4	2 h18 m	12200	32.1	1.28	57	26	313	0.81	143	105	n.t.	7.231	−8.2
	4 h40 m	n.t.	n.t.	1.28	n.t.	n.t.	n.t.	n.t.	138	72	n.t.	7.437	−2.8
	10 h05 m	7100	13.6	1.83	322	188	595	1.01	142	87	47	7.143	−9.6
	15 h37 m	7000	8.1	1.57	1570	895	2033	0.99	149	168	n.t.	7.334	−6.6
	22 h46 m	1430	10.1	2.70	5860	3320	6750	n.t.	173	125	n.t.	7.421	−3.1
5	11 h36 m	15600	17.1	1.39	397	217	728	2.72	144	n.t.	74	n.t.	−8.1
	13 h45 m	12400	11.5	1.80	289	155	579	3.59	138	324	159	7.069	−13.4

ALT, alanine aminotransferase (U/L); AST, aspartate aminotransaminase (U/L); BE, base excess (mmol/L); Cre, creatinine (mg/dL); Glu, glucose (mg/dL); LDH, lactate dehydrogenase (U/L); Na, sodium (mEq/L); NH_3, ammonia (μg/dL); PLT, platelet (*10^4/μL); PT/INR, prothrombin time/international normalized ratio; WBC, white blood cell (/μL); n.t., not tested. () indicated units.

The patients presented here were also treated with interventions more specific to AE, including HDS, TTM, and CHDF within approximately 12 h of symptom onset. However, these treatments were not effective, despite the fact that HDS in case 3, for example, was initiated within only 4 h of symptom onset. It has been reported that TTM or steroid administration within 24 h of initial symptom onset is related to better outcome of AE without AST elevation, or ANE without brainstem lesions [4,9]. Moreover, TTM for AE applied within 12 h of initial neurological signs is likely to be associated with better prognosis [18]. From the viewpoint of cerebral protection against acute brain injury, previous reports have indicated that successful interventions are often initiated only a few hours after the onset of hypoxic ischemic encephalopathy or acute ischemic stroke [19,20]. It has also been reported that in hypoxic ischemic encephalopathy, secondary deterioration at 6–15 h after asphyxia often occurred, marked by delayed seizures, secondary cytotoxic edema (cell swelling), accumulation of excitotoxins, and failure of cerebral mitochondrial activity [21].

In cases 1 and 3 in the present study, specific intervention for AE was initiated before definite diagnoses of AE. In contrast, HDS and/or TTM were initiated after diagnoses of AE in cases 2 and 4. In a review of eight patients, Rinka et al. reported that patient condition was already critical when they met the HSES criteria; thus among these criteria, platelet count, hemoglobin, DIC and renal function impairment were not useful [22]. Given these discussions of the timing of clinical events relative to onset, we consider that early intervention before an AE diagnosis is important to rescue some patients from fatal AE.

4.2. Laboratory data 24 h after symptom onset

Leakage of liver enzymes including AST, ALT, and lactate dehydrogenase (LDH) increased continuously in the cases herein presented. Regardless of treatment, the AST level rose slightly 3 h after symptom onset, and further increased 4–6 h after onset. It has also previously been reported that AST levels might predict poor AE outcomes [5,10,23]. In the present study, liver enzymes increased rapidly in the relative early reassessment of liver enzymes in cases 1 and 4. This emphasizes the importance of reassessing laboratory data 4–6 h after symptom onset in cases with continuing impaired consciousness, even should assessment be normal within 3 h after symptom onset.

In all cases considered here, creatinine was also continuously elevated above the 97.5 percentile of standard values by age. Creatinine may therefore be elevated in patients with a particularly poor prognosis, rendering it useful as a potential biomarker. Previous reports have further indicated that creatinine may help to differentially diagnose AE and prolonged FS, or predict poor acute encephalopathy with biphasic seizures and late reduced diffusion outcomes [23,24]. Moreover, creatinine, which is produced from creatine stored in the brain under excitotoxic conditions, is released into the blood when the blood brain barrier is injured [25,26].

In nearly all of the cases herein discussed, sodium levels did not fall below normal levels, and increased

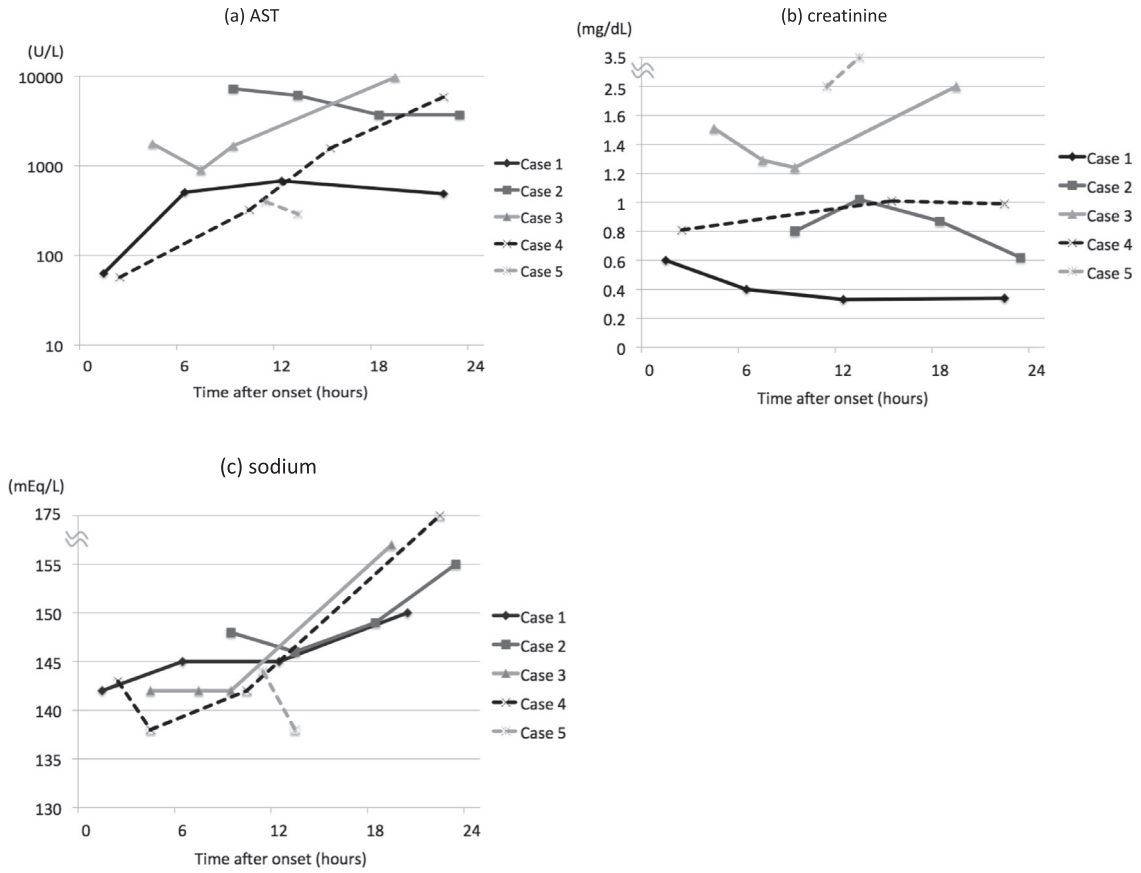

Fig. 2. Levels of aspartate aminotransferase (AST), creatine, and sodium within 24 h of symptom onset. (a) Initial AST levels were already elevated, though only slightly, in cases that were tested within 3 h of symptom onset. Four hours after symptom onset, AST levels increased rapidly in all patients. (b) For all cases, creatinine levels were continuously elevated above initial values. (c) Initial sodium levels were above 141 mEq/L and increased gradually within 24 h of symptom onset in all cases.

gradually with time. Sodium has rarely been reported to serve as a predictive factor for a poor AE prognosis, though it has been suggested to be a predictive factor for ICU mortality (APACHE II) [27]. It has also been reported that sodium levels tend to be low in individuals with FS [28]. Sodium may therefore serve as a useful factor for distinguishing between fatal AE and FS: in particular sodium increases on reassessment might be associated with fatal AE.

In the five cases reported here, abnormal laboratory findings including liver enzymes, creatinine, and sodium were identified earlier than abnormal brain imaging findings. Therefore, we considered that these changes in laboratory data such as liver enzymes, creatinine and sodium might be explained by a severe MOF rather than by encephalopathy.

5. Limitations

The findings presented here were subject to the limitation inherent to the study's retrospective clinical design. Assessment of laboratory data, EEG, and brain imaging was performed when the physician judged it necessary and not according to a fixed schedule. Further, this report documents a single-center study; thus, only a small number of patients were included. The heterogeneous population of patients with three different subtypes of AE presents a further limitation, but this heterogeneity is representative of clinical practice because it is often difficult to diagnose subtypes of AE at the early stages of the disease, even for fatal cases. A larger prospective study is therefore necessary to predict mortality and estimate the effectiveness of early intervention.

6. Conclusions

Although these results should be cautiously interpreted owing to the limitations listed, we were able to uncover some relevant information. Our findings clarified that clinical events such as DIC, MOF, and shock were identified before either brain edema on CT, or definitive diagnosis of AE. We also found that liver enzymes and creatinine levels were elevated a few hours after initial symptom onset, whereas sodium levels increased gradually as the condition progressed. Effective

interventions remain elusive, as does understanding of the usefulness of early intervention prior to a definitive diagnosis of AE. However, it is clear that the time window to rescue patients from fatal AE is relatively short.

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